



## Cytokine and CAM Antagonists and Related Agents Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Rheumatoid Arthritis (RA)	Juvenile Idiopathic Arthritis (JIA)	Ankylosing Spondylitis (AS)	Plaque Psoriasis Moderate to severe in candidates for systemic therapy or phototherapy	Psoriatic Arthritis (PsA)	Crohn's Disease (CD) Reduce signs and symptoms and inducing and maintaining clinical response in patients with moderately to severely active Crohn's Disease	Ulcerative Colitis	Cryopyrin-Associated Periodic Syndromes (CAPS)
<b>Anti-TNF Biologics</b>									
adalimumab <sup>a,b</sup> (Humira®) <sup>1</sup>	AbbVie	X	X (≥ 2 years)	X	X	X	X (≥ 6 years)	X	--
certolizumab pegol (Cimzia®) <sup>2</sup>	UCB	X	--	X	--	X	X	--	--
etanercept <sup>b,c</sup> (Enbrel®) <sup>3</sup>	Amgen	X	X (≥ 2 years)	X	X	X	--	--	--
golimumab SC <sup>d,e,f</sup> (Simponi®) <sup>4</sup>	Janssen Biotech	X	--	X	--	X	--	X	--
golimumab IV <sup>e</sup> (Simponi® Aria®) <sup>5</sup>	Janssen Biotech	X	--	--	--	--	--	--	--
infliximab <sup>e,g</sup> (Remicade®) <sup>6</sup>	Janssen Biotech	X	--	X	X	X	X (≥ 6 years)	X (≥ 6 years)	--
<b>Other Biologic Agents</b>									
abatacept <sup>b,h</sup> (Orencia®) <sup>7</sup>	Bristol-Myers Squibb	X	X (≥ 6 years) (IV only)	--	--	--	--	--	--
anakinra <sup>i</sup> (Kineret®) <sup>8</sup>	Sobi	X	--	--	--	--	--	--	X (pediatrics)
canakinumab <sup>j</sup> (Ilaris®) <sup>9</sup>	Novartis	--	X (≥ 2 years)	--	--	--	--	--	X (≥ 4 years)

IV = intravenous; SC = subcutaneous

### FDA-Approved Indications (continued)

Drug	Manufacturer	Rheumatoid Arthritis (RA)	Juvenile Idiopathic Arthritis (JIA)	Ankylosing Spondylitis (AS)	Plaque Psoriasis Moderate to severe in candidates for systemic therapy or phototherapy	Psoriatic Arthritis (PsA)	Crohn's Disease (CD) Reduce signs and symptoms and inducing and maintaining clinical response in patients with moderately to severely active Crohn's Disease	Ulcerative Colitis	Cryopyrin-Associated Periodic Syndromes (CAPS)
Other Biologic Agents (continued)									
ixekizumab (Taltz®) <sup>10</sup>	Eli Lilly	--	--	--	X	--	--	--	--
rilonacept <sup>k</sup> (Arcalyst®) <sup>11</sup>	Regeneron	--	--	--	--	--	--	--	X (≥ 12 years)
secukinumab (Cosentyx®) <sup>12</sup>	Novartis	--	--	X	X	X	--	--	--
tocilizumab <sup>l</sup> (Actemra®) <sup>13</sup>	Genentech	X	X (≥ 2 years) (IV only)	--	--	--	--	--	--
ustekinumab <sup>f,m</sup> (Stelara®) <sup>14</sup>	Janssen Biotech	--	--	--	X	X	--	--	--
vedolizumab <sup>n</sup> (Entyvio®) <sup>15</sup>	Takeda	--	--	--	--	--	X	X	--
Non-biologic Agents									
apremilast (Otezla®) <sup>16</sup>	Celgene	--	--	--	X	X	--	--	--
tofacitinib <sup>o</sup> (Xeljanz®, Xeljanz XR) <sup>17</sup>	Pfizer	X	--	--	--	--	--	--	--

IV = intravenous; SC = subcutaneous

- a. In CD, adalimumab is indicated for reducing signs and symptoms and inducing clinical remission in patients if they have an inadequate response to conventional therapy or a diminished response to or are intolerant to infliximab. Adalimumab is indicated in moderate to severe ulcerative colitis for patients who have had an inadequate response to immunosuppressants, such as corticosteroids, azathioprine, or 6-mercaptopurine (6-MP). The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF blockers. Adalimumab is also indicated for the treatment of moderate to severe hidradenitis suppurativa (HS) and non-infectious intermediate, posterior, and panuveitis.
- b. Abatacept, adalimumab, and etanercept are approved for the treatment of polyarticular JIA in children 6 years and above for abatacept and 2 years of age and above for adalimumab and etanercept.
- c. In psoriatic arthritis and RA, etanercept may be used with or without methotrexate.
- d. Golimumab subcutaneous is indicated in adult patients with moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine (6-MP) for inducing and maintaining clinical response, improving endoscopic appearance of the mucosa during induction, inducing clinical remission, or achieving and sustaining clinical remission in induction responders.
- e. In RA, infliximab and golimumab (Simponi and Simponi Aria) are indicated only in combination with methotrexate.
- f. In PsA, ustekinumab and golimumab may be used alone or in combination with methotrexate.
- g. In CD, infliximab is indicated for patients who have had an inadequate response to conventional therapy; reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing CD. Likewise, in UC, it is indicated for those with an inadequate response to conventional therapy.
- h. In RA, abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists. Abatacept should not be administered concomitantly with TNF antagonists or with anakinra.
- i. In RA, anakinra is indicated only for patients 18 years of age or older who have had an inadequate response to one or more DMARDs; it may be used alone or in combination with DMARDs except TNF antagonists. Anakinra is approved for the treatment of CAPS associated with Neonatal Onset Multisystem Inflammatory Disease (NOMID).
- j. Canakinumab is approved for the treatment of systemic JIA in patients aged 2 years and older.
- k. Rilonacept is approved for patients with CAPS, including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS).
- l. In RA, tocilizumab is indicated for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more DMARDs. In RA, tocilizumab may be used alone or in combination with methotrexate or other DMARDs. Intravenous tocilizumab is indicated for both systemic and polyarticular JIA in children 2 years of age and above. Tocilizumab prefilled syringes for subcutaneous injection are not approved for JIA.
- m. Ustekinumab should be given via subcutaneous route of administration under supervision by a physician and administered by a health care professional or by self-administration after training, if deemed appropriate.
- n. Vedolizumab is approved for treatment of moderately to severely active UC in patients who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator, or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. Vedolizumab is approved for treatment of moderately to severely active CD in patients who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator, or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.
- o. In RA, tofacitinib is indicated for the treatment of adult patients with moderately to severely active disease who have had an inadequate response or are intolerant to methotrexate. It may be used as monotherapy or in combination with methotrexate or other DMARDs. Tofacitinib should not be used in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine.

## OVERVIEW

Cytokines and cell-adhesion molecules (CAMs) are chemical mediators involved in inflammatory processes throughout the body.

### Cytokines

Cytokines are small proteins secreted in response to an immune stimulus for the purpose of mediating and regulating immunity, inflammation, and hematopoiesis. Cytokines are derived from monocytes and macrophages and induce gene expression of a number of proteins that contribute to the inflammatory response. The actions of the individual cytokines are widely varied, including stimulating production of other cytokines and increased adhesion molecule expression and activate B cells, T cells, and natural killer cells. They contribute to fibrosis and tissue degeneration associated with chronic inflammation, primarily by inducing the proliferation of fibroblasts and collagenase. The pro-inflammatory cytokines, tumor necrosis factor (TNF), and interleukin (IL)-1, are involved in tissue destruction in many chronic inflammatory diseases affecting various organs.<sup>18</sup>

TNF $\alpha$  and TNF $\beta$  are closely related proteins recognized by the same cell surface receptor. TNF $\alpha$  is overproduced in the joints of patients with rheumatoid arthritis (RA) and is increased in the synovial fluid and synovium in patients with psoriatic arthritis (PsA) and in the skin of psoriatic lesions.<sup>19,20,21,22,23</sup> Increased expression of TNF $\alpha$  has been reported in the serum, synovium, and sacroiliac joints in patients with ankylosing spondylitis (AS).<sup>24,25,26,27,28</sup> TNF $\alpha$  also has a role in Crohn's disease. IL-1 plays a major role in the promotion of rheumatic inflammation.<sup>29,30</sup> It promotes inflammation, as well as bone and cartilage resorption, and is present in increased concentrations in the synovia of patients with RA.<sup>31</sup> Over-expression of IL-12 and IL-23 have been implicated in the pathogenesis of psoriasis.<sup>32</sup> IL-12 induces and sustains TH1 immune responses leading to the secretion of interferon and the homing of T cells to the skin. IL-23 maintains chronic autoimmune inflammation via the induction of IL-17, regulation of T memory cells, and direct activation of macrophages. Ustekinumab (Stelara) is an antagonist of IL-12 and IL-23. IL-6 has a wide range of biological activities in immune regulation, hematopoiesis, inflammation, and oncogenesis.<sup>33</sup> Overproduction of IL-6 has been linked to various inflammatory, auto-immune, and malignant diseases. Tocilizumab (Actemra) is an IL-6 receptor inhibitor.

### Cell Adhesion Molecules

Cell adhesion molecules (CAMs) are cell surface proteins involved in the binding of cells, usually leukocytes, to each other, endothelial cells, or the extracellular matrix.<sup>34</sup> Specific signals produced in response to wounds and infection control the expression and activation of these molecules. The interactions and responses initiated by binding of these CAMs to their receptors/ligands play important roles in the mediation of the inflammatory and immune reactions that constitute one line of the body's defense against these insults.

Most of the CAMs characterized so far fall into 3 general families of proteins: the immunoglobulin (Ig) superfamily, the integrin family, and the selectin family.<sup>35</sup> The Ig superfamily of adhesion molecules bind to integrins on leukocytes and mediate their flattening onto the blood vessel wall with their subsequent extravasation into surrounding tissue. The integrin family of CAMs consists of an  $\alpha$  chain and a  $\beta$  chain that mediate cell-to-cell interactions, such as leukocyte adherence to the vascular endothelium. Different sets of integrins are expressed by different populations of leukocytes to provide specificity for binding to different types of CAMs expressed along the vascular endothelium.

The selectin family is involved in the adhesion of leukocytes to activated endothelium followed by extravasation through the blood vessel walls into lymphoid tissues and sites of inflammation. Other proteins that are functionally classified as CAMs are involved in strengthening the association of T cells with antigen-presenting cells or target cells, in T cell activation, and in recirculating lymphocytes back to the circulation via the lymphatic system.

Different CAMs have been implicated in inflammatory diseases (e.g., psoriasis), fibrotic diseases (e.g., degenerative diseases of the lung, liver, and kidney), and autoimmune diseases (e.g., RA).<sup>36</sup> Vascular CAM-1 has been implicated in interactions between leukocytes and connective tissue, including RA synovial tissue fibroblasts. Such interactions within the synovium contribute to RA inflammation.<sup>37</sup> In psoriatic skin, intercellular CAM-1 (ICAM-1) cell surface expression is upregulated on endothelium and keratinocytes. Activation of T lymphocytes involves the interaction between lymphocyte function-associated antigen type 3 (LFA-3) on antigen-presenting cells and CD2 on T lymphocytes. This lymphocyte activation and trafficking to skin play a role in the pathophysiology of chronic plaque psoriasis.

## Role in Therapy

The American College of Rheumatology (ACR) updated the guidelines for the management of RA in 2015.<sup>38</sup> The guidelines describe the use of agents in early (< 6 months) and established (≥ 6 months) RA. The revised guidelines focus on a treat-to-target approach based on mutual determination of a target between the patient and clinician.

In patients with early symptomatic RA, the guidelines recommend use of a disease modifying antirheumatic drug (DMARD) monotherapy (methotrexate [MTX] preferred) over double or triple therapy in patients who have never taken a DMARD, regardless of disease severity. If disease activity remains moderate or high despite DMARD treatment, the use of combination DMARDs, an anti-TNF agent, or a non-TNF biologic (all with or without methotrexate) is preferred over DMARD monotherapy. While there is no particular order to this recommendation, they do recommend the use of anti-TNF agents over tofacitinib (Xeljanz, Xeljanz XR), with or without methotrexate. Glucocorticoids may be added if disease activity remains moderate or high despite DMARD or biologic therapy and for disease flares.

In patients with established RA, ACR recommendations are similar.<sup>39</sup> They recommend use of DMARD monotherapy (methotrexate preferred) over combination therapy or tofacitinib in patients who have never taken a DMARD, regardless of disease severity. If disease activity remains moderate or high despite DMARD treatment, the use of combination DMARDs, an anti-TNF agent, a non-TNF biologic, or tofacitinib (all with or without methotrexate) is preferred over DMARD monotherapy. In addition, if the patient is using an anti-TNF agent and not taking a DMARD and disease activity remains moderate or high, the addition of a DMARD is recommended over anti-TNF agent monotherapy. If disease activity remains moderate or high despite anti-TNF monotherapy, use of a non-TNF biologic (with or without methotrexate) is preferred over another anti-TNF agent or tofacitinib. Likewise, if disease activity remains moderate or high despite non-TNF biologic use, an alternative non-TNF biologic (with or without methotrexate) is preferred over tofacitinib. Non-TNF biologics are also preferred over tofacitinib or another anti-TNF agent for sequential anti-TNF agent failures. Thus, in general, tofacitinib is an alternative in the case of multiple anti-TNF and non-TNF biologic failures and most treatments are appropriate with or without methotrexate. Similar to early RA, short-term glucocorticoids may be used for multiple treatment failures or for disease flares in experienced RA. If disease activity is low, it is

appropriate to continue treatment; if the disease is in remission, it is appropriate to taper therapy but not discontinue all treatments.

Traditional DMARDS (non-biologics) included in these guidelines are hydroxychloroquine (Plaquenil®), leflunomide (Arava®), methotrexate, and sulfasalazine (Azulfidine®).<sup>40</sup> Anti-TNF biologics include adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), and infliximab (Remicade). Non-TNF biologics include abatacept (Orencia), rituximab (Rituxan®), and tocilizumab (Actemra). Anakinra (Kineret) was excluded from the guidelines due to infrequent use and limited data.

A consensus statement on the biologic agents for the treatment of rheumatic diseases was developed in conjunction with the 2012 International Annual Workshop on Advances in Targeted Therapies.<sup>41</sup> Evidence for the efficacy and safety of the biologic agents for the treatment of various diseases was reviewed. Anti-TNF agents used in combination with methotrexate yield better results in the treatment of RA than monotherapy; adalimumab, certolizumab, and etanercept are approved as monotherapy or combination therapy for RA; infliximab and golimumab are only approved for use with methotrexate for RA in the U.S. There is no evidence that any 1 TNF antagonist should be used before another for the treatment of RA or juvenile idiopathic arthritis (JIA), except with systemic-onset JIA, when anakinra may be effective. There is no evidence that any 1 TNF antagonist is more effective than any other for the treatment of RA or AS. Indirect comparisons showed similar efficacy of abatacept compared with rituximab, tocilizumab, and golimumab in RA patients with incomplete response to TNF antagonists; however, TNF agents were more effective than abatacept in incomplete responders to methotrexate. A recent meta-analysis demonstrated that anakinra is less effective than the TNF antagonists in treating RA. Tocilizumab has not been compared directly with TNF inhibitors; however, meta-analysis comparisons show similar efficacy to other biological agents.

The Medical Letter's 2014 review for RA drugs recommends that TNF antagonists (etanercept, infliximab, adalimumab, golimumab, infliximab, and certolizumab pegol) are typically the first-line biologic agents prescribed after an inadequate response to a DMARD; they may be given as monotherapy or in combination with methotrexate.<sup>42</sup> For patients who do not respond adequately to a TNF antagonist, switching to another TNF antagonist or a non-TNF biologic agent may be effective. The combination of a biologic agent with a DMARD (usually methotrexate) offers better disease control without a substantial increase in toxicity and is now commonly used to achieve remission. Combinations are used particularly for patients with highly active disease, a long duration of disease, or with clinical features that indicate a poor prognosis. Aggressive early therapy with methotrexate and/or a biologic agent results in longer disease-free remissions, less joint destruction, and a better quality of life.

ACR's guidelines on JIA recommend initial therapy with anakinra, glucocorticoid monotherapy, or nonsteroidal anti-inflammatory drugs (NSAIDs) based on synovitis disease severity in active systemic disease.<sup>43</sup> Continued disease activity may be treated with canakinumab, tocilizumab, methotrexate, leflunomide, or an anti-TNF agent following anakinra monotherapy; anakinra, canakinumab, tocilizumab, methotrexate, or leflunomide following glucocorticoid monotherapy; or anakinra, glucocorticoid monotherapy, canakinumab, or tocilizumab following NSAID treatment. Initial treatment options for patients without active systemic features and varying degrees of synovitis include methotrexate, leflunomide, NSAID monotherapy, or intra-articular glucocorticoid injections. Continued therapy depends on response to initial therapy and disease severity, and includes abatacept, anakinra,

tocilizumab, anti-TNF agents, methotrexate, and leflunomide. An update to these guidelines is anticipated in 2018.<sup>44</sup>

Systemic therapy for plaque psoriasis may include apremilast, methotrexate, cyclosporine, acitretin (Soriatane® CK Convenience Kit), methoxsalen (Oxsoalene® Ultra), and the biologic agents, adalimumab, etanercept, infliximab, secukinumab, and ustekinumab. The American Academy of Dermatology (AAD) guidelines for the management of psoriasis and psoriatic arthritis, section 6, states there is no specific sequence in which anti-TNF agents should be used in patients with moderate to severe chronic plaque psoriasis without psoriatic arthritis.<sup>45,46</sup> Monotherapy with adalimumab, etanercept, infliximab, and ustekinumab are listed as acceptable first-line agents after failure of topical therapy alone when phototherapy is not available. However, the guidelines note that in non head-to-head phase 3 trials of the individual agents, infliximab clears cutaneous psoriasis in the highest proportion of patients and with the greatest rapidity, followed by adalimumab and then etanercept. In patients with moderate to severe psoriatic arthritis, methotrexate, adalimumab, etanercept, golimumab, infliximab, or a combination of methotrexate plus an anti-TNF agent is considered first-line treatment. These guidelines were published prior to the approval of apremilast, ixekizumab, and secukinumab. The National Psoriasis Foundation consensus statement from 2008 recommends that all patients receiving systemic or biologic agents for psoriasis be screened for latent TB infection prior to initiating any immunologic therapy.<sup>47</sup> Delaying immunologic therapy until latent TB infection prophylaxis is completed is preferable. Patients with a positive tuberculin skin test should be treated with a full course of latent TB infection prophylaxis before beginning immunosuppressive or immunomodulatory treatment. However, if the patient is adhering to his or her prophylactic regimen and is appropriately tolerating the regimen, therapy may be started after 1 to 2 months, if the clinical condition requires treatment. Treatment guidelines from ACR for psoriatic arthritis are in development; a published guideline is anticipated in 2018.<sup>48</sup>

In 2015, the ACR, Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) published guidelines on the treatment of ankylosing spondylitis (AS) and nonradiographic axial spondylarthritis.<sup>49</sup> For AS, the guidelines recommend NSAIDs as a primary treatment with anti-TNF agents as alternatives in patients with continued activity despite NSAID treatment. No particular anti-TNF agent is preferred over another, except in patients with comorbid inflammatory bowel disease or recurrent iritis, in which monoclonal antibodies should be used (e.g., infliximab or adalimumab over etanercept).

The 2014 American Gastroenterology Association (AGA) practice guidelines for the management of Crohn's disease in adults recommends using anti-TNF drugs to induce remission in patients with moderately severe Crohn's disease (strong recommendation, moderate-quality evidence).<sup>50</sup> The anti-TNF drugs infliximab or adalimumab are more likely than placebo to induce remission in patients with moderately severe Crohn's disease refractory to other therapies, including mesalamine, antibiotics, corticosteroids, and immunomodulators. A key feature of these agents is the ability to induce remission in patients who have not responded to treatment with corticosteroids or immune modulators. These guidelines state certolizumab pegol has not been found to be more effective than placebo in inducing remission in patients with moderately severe Crohn's disease and is approved for reducing signs and symptoms and maintaining response only. Citing the results of the SONIC trial where the combination of infliximab and azathioprine was superior to infliximab alone in inducing remission in patients with moderately severe Crohn's disease who had not previously received either therapy, the guideline suggests using anti-TNF drugs in combination with thiopurines over anti-TNF

monotherapy to induce remission in patients who have moderately severe Crohn's disease (weak recommendation, moderate-quality evidence). The anti-TNF drugs are superior to placebo in maintaining remission among patients with moderately severe Crohn's disease who had remission induced by these drugs. The data indicate that infliximab and adalimumab, as well as certolizumab, have substantial and similar benefits in the maintenance setting.

The 2009 American College of Gastroenterology (ACG) guidelines for Crohn's Disease recommend the use of anti-TNF agents (e.g., infliximab, certolizumab pegol, adalimumab) for the treatment of moderate to severe disease in patients who have not responded to corticosteroids or immunosuppressive agents.<sup>51</sup> They may also be used in patients with contraindications to steroid therapy. One is not preferred over another, but more data were available with infliximab at the time of guideline production. **Updated guidelines are in progress.**

The 2010 ACG guidelines for ulcerative colitis (UC) state infliximab is effective in maintaining and improving remission in patients with mild to moderate extensive (extends proximal to the descending colon) colitis who responded to an infliximab induction regimen (Evidence A).<sup>52</sup> These guidelines also state infliximab is indicated for the management of patients with severe colitis who continue to have severe symptoms despite optimal doses of oral corticosteroids. These guidelines do not address adalimumab or certolizumab pegol and in those with severe colitis who continue to have severe symptoms despite optimal doses of oral corticosteroids. **Updated guidelines are in progress.**

**The AGA has not published guidelines for UC, but they have created a clinical algorithm.<sup>53</sup> The clinical algorithm recommends an anti-TNF agent with or without a thiopurine; or vedolizumab (Entyvio) with or without thiopurine or methotrexate, for maintenance therapy in high-risk outpatients following induction therapy. If induction therapy is done with either an anti-TNF agent or vedolizumab, these agents should be continued. In cases of loss of response to an anti-TNF agent, the anti-TNF dose should be optimized, and a switch within class, the addition of an immunomodulator, or a switch to vedolizumab may be considered. In cases of loss of response to vedolizumab, the dose should be optimized, and a switch to an anti-TNF agent may be considered. Infliximab may be used in inpatients who have failed IV steroids and for maintenance of remission.**

In a 2014 review of drugs for inflammatory bowel disease by The Medical Letter, multiple agents are addressed and the agents specific to this therapeutic class review are described below. The TNF inhibitors, infliximab, adalimumab, and certolizumab pegol, alone or in combination with azathioprine or 6-mercaptopurine, are used for treatment of moderate to severe Crohn's disease for either induction or maintenance treatment.<sup>54</sup> Vedolizumab (Entyvio) is considered an alternative agent, in addition to natalizumab (Tysabri®) and methotrexate. Infliximab may also be used in perianal or fistulizing disease for either induction or maintenance of remission. In moderate to severe ulcerative colitis, infliximab and adalimumab may be used for maintenance of remission. Alternatives include golimumab and vedolizumab, while alternatives to steroids for induction include infliximab, adalimumab, golimumab, and vedolizumab. These agents are also recommended in some mild cases that do not respond to alternative treatments (aminosalicylates). They also recommend infliximab, adalimumab, golimumab, and vedolizumab as alternatives for induction and maintenance of remission in patients with mild to moderate ulcerative colitis. For patients with moderate to severe ulcerative colitis, infliximab and adalimumab are recommended for maintenance of remission (among other options), while golimumab and vedolizumab are considered alternatives. Infliximab, adalimumab, golimumab, and vedolizumab are also considered alternatives for induction of remission in this population.

Cryopyrin-associated periodic syndromes (CAPS) includes Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and chronic infantile neurologic cutaneous articular syndrome (CINCA), which is also known as neonatal-onset multisystem inflammatory disease (NOMID).<sup>55</sup> These are hereditary periodic fever syndromes that are rare and characterized by short and recurrent severe localized inflammation and fever “attacks” that are not otherwise explained by routine childhood infections. These can occur periodically or irregularly and undergo spontaneous remission. Anakinra (Kineret), canakinumab (Ilaris), and rilonacept (Arcalyst) are approved for the treatment of CAPS in select ages. Anakinra is only approved for patients with CAPS associated with NOMID while rilonacept is approved for patients with CAPS, including FCAS and MWS.

Hidradenitis suppurativa (HS), an insidious chronic condition, affects the terminal follicular epithelium in apocrine gland-bearing skin, such as the armpits or perianal area.<sup>56,57</sup> It typically occurs in adolescents (generally after puberty) and adults, is generally diagnosed clinically, and affects approximately 1% to 2% of the U.S. population. Select signs and symptoms include erythema, raised bumps or lesions, painful lesions, and local arthritis or arthralgia. In addition to nonpharmacologic treatments, pharmacologic treatment includes anti-inflammatories, antibiotics, antiandrogens, and biologics, such as infliximab (Remicade). Surgery may also be considered in some patients. Guidelines for treatment are limited, but guidelines from the European Dermatology Forum recommend either adalimumab or infliximab in severe or refractory disease, stating adalimumab appears to be better tolerated; however, only adalimumab is approved by the FDA for this use.

Non-infectious intermediate and posterior uveitis is inflammation of the intermediate and posterior uvea while panuveitis is inflammation of the anterior chamber, vitreous humor, and choroid or retina simultaneously.<sup>58,59,60</sup> Together, these represent the most severe and highly recurrent forms of uveitis. The incidence of all cases of uveitis is approximately 15 cases per 100,000 patients per year, and anterior uveitis is the most common form of uveitis. Initial treatment is typically with topical corticosteroids. Adalimumab is generally reserved for patients with disease non-responsive to initial treatment. Other treatments include systemic glucocorticoids, immunosuppressives, and intraocular implants.

## PHARMACOLOGY<sup>61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77</sup>

### Cytokine Antagonists

Antagonists that bind cytokines or their receptors can block cytokine activity. Biologics, such as the IL-1 receptor antagonist, anakinra (Kineret), canakinumab (Ilaris), and rilonacept (Arcalyst), and anti-TNF $\alpha$  agents, adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), and infliximab (Remicade), exert their action by neutralizing the activities of the inflammatory agents IL-1 and TNF $\alpha$ , respectively. Ustekinumab (Stelara) is an IL-12 and IL-23 antagonist. Tocilizumab (Actemra) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody.<sup>78</sup> Ixekizumab (Taltz) and secukinumab (Cosentyx) are human IgG1 monoclonal antibodies that selectively bind to the interleukin-17A (IL-17A) cytokine and inhibit its interaction with the IL-17 receptor. Vedolizumab (Entyvio) is a humanized monoclonal antibody that binds to  $\alpha 4\beta 7$  integrin and blocks mucosal cell adhesion and inhibits the migration of T-lymphocytes into the gastrointestinal tissue. Apremilast (Otezla) has a substantially different mechanism; it is an oral phosphodiesterase 4 (PDE4) inhibitor, specific for cyclic adenosine monophosphate (cAMP) PDE4 inhibition. The specific mechanism by which apremilast exerts its effect is unknown.

Despite their common ability to inhibit TNF $\alpha$  bioactivity, the molecular structures and mechanisms of action of anti-TNF $\alpha$  agents are significantly different. The TNF-binding moiety of etanercept, a fusion protein, is derived from soluble TNF receptor subunits; infliximab is a chimeric (mouse-human) monoclonal antibody to TNF, while adalimumab, golimumab, and certolizumab pegol are fully human anti-TNF monoclonal antibodies.<sup>79</sup>

Cytokines secreted in response to an immune stimulus bind to receptors on cell surfaces and activate intracellular Janus kinase (JAK) proteins, which in turn activate a signaling pathway within the cell, leading to immune cell proliferation.<sup>80</sup> Over-activation of JAK can lead to inflammation and tissue destruction. Tofacitinib (Xeljanz, **Xeljanz XR**) selectively inhibits JAK1 and JAK3, thereby blocking signaling for several cytokines, including many interleukins that are integral to lymphocyte activation, proliferation, and function. In addition, inhibition of JAK1 results in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6.

## PHARMACOKINETICS<sup>81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97</sup>

Drug	Half-life (days)	Bioavailability (%)
<b>Anti-TNF Biologics</b>		
adalimumab (Humira) <sup>98</sup>	10 to 20	64 (SC)
certolizumab pegol (Cimzia)	14	80 (SC)
etanercept (Enbrel)	4.3 ± 1.3	60 (SC)
golimumab SC (Simponi)	14	53 (SC)
golimumab IV (Simponi Aria)	12 ± 3	(IV)
infliximab (Remicade)	7.7 to 9.5	(IV)
<b>Other Biologic Agents</b>		
abatacept IV (Orencia)	13.1 to 14.3	(IV)
abatacept SC (Orencia)	14.3	78.6 (SC)
anakinra (Kineret)	0.17 to 0.25	95 (SC)
canakinumab (Ilaris)	26	66 (SC)
ixekizumab (Taltz)	13	60 to 81 (SC)
rilonacept (Arcalyst)	nd	nd
secukinumab (Cosentyx)	22 to 31	55 to 77 (SC)
tocilizumab (Actemra) adults*	11 to 13 (IV)	(IV)
tocilizumab (Actemra) pediatrics*	16- 23 (IV)	(IV)
tocilizumab (Actemra) adults*	5 to 13 (SC)	80 (SC)
ustekinumab (Stelara)	14.9 to 45.6	nd
vedolizumab (Entyvio)	25	(IV)
<b>Non-biologic Agents</b>		
apremilast (Otezla)	6 to 9 hours	73 (PO)
tofacitinib (Xeljanz, Xeljanz XR)	3 hours (IR); 6 hours (ER)	74 (PO; IR); nd (ER)

nd = no data; IV = intravenous; SC = subcutaneous; PO = oral; IR = immediate-release; ER = extended-release

\*Nonlinear – concentration dependent

## CONTRAINDICATIONS/WARNINGS<sup>99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115</sup>

### TNF-blocking agents – adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), and infliximab (Remicade)

The TNF-blocking agents all have a warning stating serious and sometimes fatal infections, including bacterial, tuberculosis (TB), viral, and opportunistic invasive fungal infections, have been reported with their use. Among opportunistic infections, tuberculosis, including reactivation of latent TB, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, and pneumocystosis were the most commonly reported. Serious bacterial infections due to *Legionella* and *Listeria* have been reported. Typically, patients present with disseminated disease rather than localized disease and are on concurrent immunosuppressants, such as methotrexate or corticosteroids plus an agent in this review. Treatment with a TNF blocker should not be initiated in patients with an active infection, and the

risk/benefit ratio should be evaluated for patients with chronic or recurrent infections, exposure to TB, underlying conditions which predispose them to infections, or who have resided or traveled in areas of endemic TB or endemic mycoses. As a result, these agents must be used with caution in patients on concomitant immunosuppressive therapy and/or active or predisposition to infections. It is recommended that patients be evaluated with a TB skin test and that latent TB infections be treated prior to therapy. Monitor all patients during therapy for TB even if the initial latent TB test was negative. Use of TNF blockers should be discontinued if a patient develops a serious infection or sepsis. Anti-TB therapy prior to initiation of a TNF blocker may be considered in select patients. Data obtained from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) suggest that adalimumab and infliximab carry a higher risk of serious infections than etanercept.<sup>116</sup>

Use caution when switching between one biologic DMARD to another as overlapping biologic activity may increase the risk of infection.

Other therapeutic infectious agents (e.g., BCG bladder instillation for the treatment of cancer) could result in infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with TNF blockers.

Use of TNF blockers has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Carriers of HBV who require treatment with a TNF blocker should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of treatment. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Serious infections were seen in clinical studies with concurrent use of anakinra and etanercept, with no added benefit. Due to the nature of the adverse reactions seen with this combination therapy, similar toxicities may result from combination of anakinra and other TNF-blocking agents.

Patients at greater risk of infection may include patients older than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants, such as corticosteroids or methotrexate. The risks and benefits of treatments with TNF antagonists should be considered prior to initiating therapy in patients with chronic or recurrent infection, with prior exposure to tuberculosis, with a history of an opportunistic infection, or patients who have resided or traveled to areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, or patients with underlying conditions that may predispose them to infection, such as poorly controlled diabetes.

The TNF blockers also possess a warning concerning the increased incidence of lymphoma in patients receiving these agents, especially in patients with active RA. In the controlled portions of clinical trials of some TNF-blocking agents, more malignancies (excluding lymphoma and nonmelanoma skin cancer) have been observed in patients receiving those TNF blockers compared with control patients. The potential role of TNF-blocking therapy in the development of malignancies is not known.

Hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, has been reported in patients treated with TNF blockers. Nearly all of the reported TNF blocker-associated cases of HSTCL have occurred in patients with Crohn's disease, with some occurring in ulcerative colitis patients. The majority were in adolescent and young adult males. Almost all patients had received azathioprine (AZA) or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis.

In November 2009, the risk of lymphoma and other malignancies, some fatal, reported in children and adolescent patients treated with TNF blockers was added to the boxed warning for TNF blockers. Approximately half of the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. Cases of acute and chronic leukemia have been reported in association with post-marketing TNF blocker use in RA and other indications.

The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Acute and chronic leukemia have also been reported with TNF blocker use in RA and other indications. Even in the absence of TNF blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer. As of November 2011, the FDA is requiring manufacturers of TNF blockers to perform enhanced safety surveillance on these products.<sup>117</sup>

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Patients with psoriasis should be monitored for non-melanoma skin cancers, especially in those patients with a history of prolonged phototherapy treatment. Non-melanoma skin cancers were more common in patients with previous phototherapy in the maintenance trials of infliximab for the treatment of psoriasis.

In a clinical trial using infliximab in patients with moderate to severe COPD, an increase in malignancies, the majority being of the lung or head and neck region, were reported in the patients receiving infliximab compared to control patients. All patients had a history of heavy smoking. Providers should use caution in using infliximab in patients with moderate to severe COPD.

In a randomized, placebo-controlled trial with 180 patients with Wegener's granulomatosis, etanercept-treated patients experienced more non-cutaneous solid malignancies than patients who received placebo. Clinical outcomes with etanercept plus cyclophosphamide, methotrexate, and corticosteroids did not improve compared to the 3-drug treatment alone. Etanercept is not indicated for the management of Wegener's granulomatosis.

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, and thrombocytopenia) have been infrequently reported with certolizumab pegol. Use caution in patients being treated with TNF blockers who have ongoing, or a history of, significant hematologic abnormalities.

Cases of worsening congestive heart failure (CHF), some with a fatal outcome, and new onset CHF have been reported with TNF blockers. Clinical trials of TNF blockers show a higher rate of serious CHF-

related adverse reactions. Physicians should exercise caution when using TNF blockers in patients who have heart failure and monitor them carefully.

In 2 clinical trials evaluating the use of etanercept for the treatment of heart failure, 1 study suggested higher mortality in the etanercept-treated patients compared to placebo. There have been post-marketing reports of worsening of CHF, with and without precipitating factors, in patients taking etanercept. New onset CHF (<0.1%) has been reported, including in patients without known pre-existing cardiovascular disease. Use etanercept with caution in patients with a history of CHF.

Infliximab at doses > 5 mg/kg is contraindicated in patients with moderate to severe heart failure. In a randomized study evaluating infliximab in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), infliximab treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure.

Treatment with agents that inhibit TNF has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system (CNS) demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed. Exercise caution with the use of TNF blockers in patients with pre-existing or recent-onset CNS demyelinating disorders. Treatment with TNF blockers may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with TNF blockers, treatment should be discontinued, and the patient should be carefully evaluated.

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with TNF blockers. If an anaphylactic or other serious allergic reaction occurs, administration should be discontinued immediately and appropriate therapy instituted. The offending TNF blocker should not be readministered.

Infliximab has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infliximab infusion. Serum sickness-like reactions have been observed in patients after initial infliximab therapy (e.g., as early as after the second dose), and when infliximab therapy was reinstituted following an extended period without infliximab treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema, and/or dysphagia. In RA, Crohn's disease, and psoriasis clinical trials, readministration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment. In general, the benefit-risk of readministration of infliximab after a period of no treatment, especially as a re-induction regimen given at weeks 0, 2, and 6, should be carefully considered. If infliximab maintenance therapy for psoriasis is interrupted, infliximab should be restarted as a single dose followed by maintenance therapy.

Reports of severe hepatic reactions, including acute liver failure, have been reported in patients receiving TNF blockers.

In a small study of 48 hospitalized patients treated with etanercept or placebo for moderate to severe alcoholic hepatitis, the mortality rate in patients treated with etanercept was similar to patients

treated with placebo at 1 month, but significantly higher after 6 months. Physicians should use caution when using etanercept in patients with moderate to severe alcoholic hepatitis.

It is recommended that JIA patients, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating therapy.

Patients on adalimumab, etanercept, and golimumab may receive concurrent vaccinations, except for live vaccines. Patients with a significant exposure to varicella virus should temporarily discontinue etanercept therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Patients treated with certolizumab pegol may receive vaccinations, except for live or live attenuated vaccines. In clinical trials, similar proportions of patients developed protective levels of anti-vaccine antibodies between certolizumab pegol and placebo treatment groups; however, patients receiving certolizumab pegol and concomitant methotrexate had a lower humoral response compared with patients receiving certolizumab pegol alone. The clinical significance of this is unknown. No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving certolizumab pegol.

Live vaccines are not recommended for concurrent use with infliximab. A fatal outcome due to disseminated TB infection was reported in an infant who received a TB vaccine after *in utero* exposure to infliximab. At least a 6-month waiting period following birth is recommended prior to live vaccine administration in infants with *in utero* exposure to infliximab. The safety of live or live-attenuated vaccines in infants who were exposed to other anti-TNF agents *in utero* is unknown; a risk-benefit assessment should occur prior to vaccinating these infants.

Etanercept is contraindicated in patients with sepsis.

### **abatacept (Orencia)**

Abatacept should not be administered to patients with known hypersensitivity to abatacept or any of its components.

In clinical trials, patients receiving concomitant abatacept (via intravenous administration) and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively). No additional efficacy was observed with concomitant administration; therefore, concurrent abatacept and TNF antagonist therapy is not recommended. Serious infections, including sepsis and pneumonia, have been reported in patients receiving abatacept. In clinical studies, the safety experience for abatacept was similar for both subcutaneously and intravenous administered dosages.

Patients should be screened for latent tuberculosis (TB) infection prior to initiating therapy with abatacept. Abatacept has not been studied in patients with a positive TB screening test; therefore, safety of abatacept in patients with latent TB is not known. Additionally, screening for hepatitis B should be performed prior to initiating therapy with abatacept according to published guidelines.

Patients with chronic obstructive pulmonary disease (COPD) reported more adverse events in clinical trials than those treated with placebo. Use caution when administering abatacept to patients with RA and COPD and monitor for worsening of their respiratory status.

Live vaccines should not be given concurrently or within 3 months of discontinuation of abatacept. Patients with JIA should be brought up-to-date with all immunizations prior to abatacept therapy. Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations.

Anaphylaxis or anaphylactoid reactions have been reported following administration of abatacept (0.074% of patients). Appropriate medical support for the treatment of hypersensitivity reactions should be available when abatacept is administered.

### **anakinra (Kineret)**

Anakinra is contraindicated in patients with known hypersensitivity to *Escherichia coli*-derived proteins or any components of the product.

Concurrent use of anakinra and etanercept therapy resulted in a higher rate of serious infections in the combination arm (7%) compared to etanercept alone (0%) without an increase in ACR response rates compared to etanercept monotherapy. Combination therapy with anakinra and TNF blockers is not recommended.

Anakinra has been associated with an increased incidence of serious infections versus placebo (2% versus 1%, respectively) and should be discontinued if a patient develops a serious infection. Treatment with anakinra should not be initiated in patients with active infections. Safety and efficacy of anakinra in immunosuppressed patients or in patients with chronic infections have not been evaluated. In patients with NOMID, if anakinra discontinuation is contemplated, the risk of NOMID flare upon discontinuation of therapy should be weighed against the potential risk of continued treatment.

### **apremilast (Otezla)**

Apremilast is contraindicated in patients with known hypersensitivity to any components of the product.

Apremilast is associated with an increased risk of depression. Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts, or other mood changes, and, if such changes occur, to contact their healthcare provider. Risks and benefits of treatment with apremilast should be carefully weighed in patients with a history of depression and/or suicidal thoughts or behavior.

During clinical trials, apremilast was associated with weight decrease. Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of apremilast.

### **canakinumab (Ilaris)**

Canakinumab is contraindicated in patients with known hypersensitivity to any components of the product. Canakinumab blocks IL-1 which may interfere with immune response to infections. Treatment with medications that work through inhibition of IL-1 has been associated with an increased risk of serious infections. Canakinumab has been associated with an increased incidence of serious infections. Physicians should exercise caution when administering canakinumab to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections. Canakinumab should be discontinued if a patient develops a serious infection and do not administer it to patients during an active infection requiring medical intervention. Live vaccines should not be given

concurrently with canakinumab. Prior to initiation of therapy with canakinumab, patients should receive all recommended vaccinations.

### **ixekizumab (Taltz)**

Ixekizumab is contraindicated in patients with serious hypersensitivity reaction to ixekizumab or to any of the excipients.

Treatment with ixekizumab may put patients at an increased risk for infection. In clinical trials, the rate of infections was higher in the ixekizumab group versus the placebo group (27% versus 23%). The types of infections that occurred more frequently in the ixekizumab group versus the placebo group included upper respiratory tract infections (which includes nasopharyngitis and rhinovirus infection), oral candidiasis, conjunctivitis, and tinea infections.

Prior to initiating treatment with ixekizumab, patients should be evaluated for TB and ixekizumab should not be given to patients with active TB infection. Anti-TB therapy should be considered prior to initiating ixekizumab in patients with a past history of latent TB or patients with active TB who have not received an appropriate course or treatment.

Patients receiving ixekizumab should be monitored for new onset IBD or exacerbations of existing disease, including CD and UC, which occurred at a greater rate with ixekizumab in placebo controlled trials.

### **rilonacept (Arcalyst)**

Rilonacept blocks IL-1 which may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking rilonacept. Discontinue treatment with rilonacept if a patient develops a serious infection and do not initiate treatment with rilonacept in patients with active or chronic infections.

Rare hypersensitivity reactions have been associated with rilonacept administration. If a hypersensitivity reaction occurs, discontinue administration of rilonacept. Live vaccines should not be given concurrently with rilonacept. Prior to initiation of therapy with rilonacept, patients should receive all recommended vaccinations.

Patients should also be monitored for changes in their lipid profiles and provided with medical treatment if warranted.

### **secukinumab (Cosentyx)**

Secukinumab may increase the risk of infections. Exercise caution when considering the use of secukinumab in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and secukinumab should be discontinued until the infection resolves.

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with secukinumab. Do not administer secukinumab to patients with active TB infection. Initiate treatment of latent TB prior to administering secukinumab. Consider anti-TB therapy prior to initiation of secukinumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving secukinumab should be monitored closely for signs and symptoms of active TB during and after treatment.

Exercise caution when prescribing secukinumab to patients with inflammatory bowel disease, as exacerbations of Crohn's disease, in some cases serious, were observed in secukinumab-treated patients during clinical trials. Patients who are treated with secukinumab and have inflammatory bowel disease should be monitored closely.

Anaphylaxis and cases of urticaria occurred in secukinumab-treated patients in the clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of secukinumab should be discontinued immediately and appropriate therapy initiated.

The removable cap of the secukinumab products contains natural rubber latex, which may cause an allergic reaction in latex-sensitive individuals. The safe use of Cosentyx Sensoready pen or prefilled syringe in latex-sensitive individuals has not been studied.

Prior to initiating therapy with secukinumab, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with secukinumab should not receive live vaccines. Non-live vaccinations received during a course of secukinumab may not elicit an immune response sufficient to prevent disease.

### **tocilizumab (Actemra)**

Tocilizumab should not be administered to patients with known hypersensitivity to tocilizumab. Patients receiving tocilizumab are at an increased risk for developing serious infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens that may lead to hospitalization or death. Most patients in clinical trials who developed serious infections were on concurrent immunosuppressants, such as methotrexate or corticosteroids. If a serious infection develops, tocilizumab should be discontinued until the infection is controlled. Infections reported included active TB, invasive fungal infections, bacterial, viral, and other infections due to opportunistic pathogens. Patients should be tested for latent TB before and during treatment with tocilizumab. In patients with chronic or recurrent infections, the risks and benefits of treatment with tocilizumab should be carefully considered prior to initiating therapy with tocilizumab. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tocilizumab, including the possibility of TB in patients who tested negative for latent TB infection prior to initiating therapy. Tocilizumab should not be initiated in patients with active infections, including localized infections. The risk and benefits of tocilizumab therapy should be considered prior to initiation of therapy. Patients with higher infection risks include those with chronic or recurrent infection, exposure to TB, history of serious or an opportunistic infection, with a history of travel or residence in areas of endemic TB or endemic mycoses, or those with underlying conditions that may predispose them to infections. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tocilizumab, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.

Cases of viral reactivation of herpes zoster have been reported. Patients who tested positive for hepatitis were excluded from clinical trials of tocilizumab.

Gastrointestinal (GI) perforation has been reported in clinical trials with tocilizumab, mostly as a result of complications of diverticulitis. Patients with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Tocilizumab therapy has been associated with a higher incidence of neutropenia and thrombocytopenia. Tocilizumab should not be initiated in patients with a low absolute neutrophil

count (ANC < 2,000/mm<sup>3</sup>) or platelet counts of < 100,000/mm<sup>3</sup>. Therapy is not recommended if the ANC during tocilizumab therapy is less than 500/mm<sup>3</sup> or platelet count falls to less than 50,000/mm<sup>3</sup>. Monitor neutrophils and platelets 4 to 8 weeks after the start of therapy and every 3 months thereafter. Dose modifications for tocilizumab are recommended based on ANC and platelet counts.

Elevations of liver transaminases were reported in clinical trials with tocilizumab but did not result in permanent or clinically evident hepatic injury. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs, such as methotrexate, were used in combination with tocilizumab. Reported elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) resolved with discontinuation of tocilizumab. Therapy with tocilizumab should not be initiated in patients with baseline elevations of ALT or AST of greater than 1.5 times the upper limit of normal. Tocilizumab is not recommended if ALT or AST exceed more than 5 times the upper limit of normal. Monitor ALT and AST levels 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, other liver function tests, such as bilirubin, should be considered. Dose modifications for tocilizumab due to elevations of ALT and/or AST are recommended. Patients with active hepatic disease or hepatic impairment should not receive tocilizumab.

Tocilizumab is associated with increases in lipid parameters including total cholesterol, triglycerides, LDL-cholesterol, and/or HDL-cholesterol. Lipid parameters should be assessed at approximately 4 to 8 weeks after initiation of tocilizumab therapy and then measured every 6 months. Patients should be managed according to clinical guidelines for hyperlipidemia.

The effect that tocilizumab has on the development of malignancies and demyelinating disorders is unknown, but malignancies, multiple sclerosis, and chronic inflammatory demyelinating polyneuropathy were reported during clinical trials. Prescribers should exercise caution in considering the use of tocilizumab in patients with pre-existing or recent onset demyelinating disorders.

Hypersensitivity reactions, including anaphylaxis, have been reported during tocilizumab infusions (0.2%) and with subcutaneous injections (0.7%). Anaphylaxis with intravenous administration has resulted in death. Reactions have occurred with a range of doses, sometimes as early as the first dose, and even in patients who have received premedication.

Tocilizumab has not been studied in combination with other biological DMARDs including TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies, and selective co-stimulation modulators. Combination therapy should be avoided as there is a possibility of increased immunosuppression and increased risk of infection.

### **tofacitinib (Xeljanz, Xeljanz XR)**

Boxed warnings include increased risk of serious and sometimes fatal bacterial, mycobacterial, fungal, and viral infections in those treated with tofacitinib. Most commonly reported serious infections included pneumonia, cellulitis, herpes zoster, diverticulitis, and urinary tract infections. Active TB was also reported. TB screening and appropriate treatment prior to initiation of tofacitinib treatment is recommended. Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with tofacitinib. The impact of tofacitinib on chronic viral hepatitis reactivation is unknown as patients who screened positive for hepatitis B or C were excluded from clinical trials. Tofacitinib should not be initiated in patients with an active infection, including localized infections. The risk and benefits of treatment should be considered when prescribing tofacitinib in

patients with a history of chronic, recurrent, or serious infection, prior exposure to TB, or a comorbid condition that predisposes them to infection.

A boxed warning also exists regarding the increased risk of malignancies, including lymphoma. The most common types of malignancies reported were lung and breast cancer. Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications.

Ten events of gastrointestinal (GI) perforations were identified (in 4,791 patients) in clinical trials with tofacitinib in RA patients. Tofacitinib should be used with caution in patients who may be at increased risk for GI perforation, such as a history of diverticulitis. New onset of abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Treatment with tofacitinib has been associated with decreases in lymphocyte, neutrophil, and red blood cell counts. It is recommended that tofacitinib not be initiated in patients with a lymphocyte count  $< 500$  cells/mm<sup>3</sup>, an ANC  $< 1,000$  cells/mm<sup>3</sup>, or a hemoglobin level  $< 9$  g/dL. In patients receiving tofacitinib, lymphocyte counts should be obtained at baseline and every 3 months thereafter. Neutrophil and hemoglobin should be monitored at baseline, 4 to 8 weeks after initiation of therapy, and every 3 months thereafter.

Tofacitinib was associated with an increased incidence of elevated liver enzymes. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of tofacitinib should be interrupted until this diagnosis has been ruled out. Treatment with tofacitinib is not recommended in patients with severe hepatic impairment.

Dose dependent increases in total cholesterol, LDL-C, and HDL-C were observed in clinical trials. Increases occurred within 1 to 3 months of the start of tofacitinib therapy and remained stable thereafter with continued treatment. No evidence for an increase in cardiovascular risk has been observed. Lipid assessments should be performed approximately 4 to 8 weeks following initiation of therapy, and patients should be managed according to clinical guidelines (e.g., National Cholesterol Educational Program [NCEP]) for the management of hyperlipidemia.

No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines to patients receiving tofacitinib. Live vaccines should not be given concurrently. Immunizations should be updated consistent with current immunization guidelines prior to initiating tofacitinib therapy.

Treatment with tofacitinib is not recommended in patients with severe hepatic impairment.

Since the extended-release formulation (Xeljanz XR) contains some non-deformable material, caution should be used when it is used in patients with pre-existing gastrointestinal narrowing due to rare reports of obstructive symptoms in this population.

## **ustekinumab (Stelara)**

Ustekinumab (Stelara) is contraindicated in patients with a history of clinically significant hypersensitivity to ustekinumab or to any of the excipients. Serious allergic reactions including angioedema and anaphylaxis have been reported with ustekinumab. Discontinue use of ustekinumab and institute appropriate therapy.

Ustekinumab may increase the risk of infections and reactivation of latent infections. Patients genetically deficient in IL-12/IL-23 are vulnerable to disseminated infections from mycobacteria, salmonella, and Bacillus Calmette-Guerin (BCG) vaccinations. It is not known whether patients with pharmacologic blockade of IL-12/IL-23 with ustekinumab will be susceptible to these types of infections. During clinical trials for the treatment of psoriasis, serious infections diagnosed included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, and sepsis. In the psoriatic arthritis trials, serious infections included cholecystitis. Ustekinumab should not be given to patients with any clinically important active infection. Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Diagnostic tests to screen for these infections should be considered, as dictated by clinical circumstances. Patients should be evaluated for tuberculosis prior to initiating therapy with ustekinumab. Do not administer ustekinumab to patients with active TB. Consider initiation of anti-TB therapy prior to ustekinumab therapy for patients with a past history of latent TB or active TB or those in who an adequate course of treatment cannot be confirmed. Prior to initiating therapy, patients should receive all age-appropriate immunizations.

As an immunosuppressant, ustekinumab may increase the risk of malignancy. There have been reports of multiple rapidly appearing cutaneous squamous cell carcinomas in patients who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving ustekinumab should be monitored for non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy, and those with a history of psoralen plus ultraviolet light (PUVA) treatment should be followed closely. The safety of ustekinumab in patients with a history of or a known malignancy has not been evaluated. Ustekinumab has not been studied beyond 2 years of use.

One case of reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in clinical trials with ustekinumab. RPLS is a neurological disorder that is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion, and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents, and immunosuppressive therapy. Fatal outcomes have been reported.

Prior to initiating therapy, patients should receive all age-appropriate immunizations.

BCG vaccines should not be given during treatment with ustekinumab or for 1 year prior to initiating treatment or for 1 year after discontinuation. Use caution when administering live vaccines to household contacts of patients receiving ustekinumab due to the potential risk of viral shedding from the household contacts and transmission to the patient. Non-live vaccinations received during ustekinumab therapy may not elicit an immune response sufficient to prevent disease.

Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab may decrease the protective effect of allergy immunotherapy and may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergy immunotherapy, particularly for anaphylaxis.

## **vedolizumab (Entyvio)**

Vedolizumab is contraindicated in patients with a history of hypersensitivity to vedolizumab or to any of the excipients. Treatment with vedolizumab is not recommended in patients with active, severe

infections until the infections are controlled. Consider withholding vedolizumab in patients who develop a severe infection while on treatment.

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system. While no cases of PML were identified among patients with at least 24 months of vedolizumab exposure, a risk of PML cannot be ruled out. Monitor patients on vedolizumab for any new onset, or worsening, of neurological signs and symptoms.

### **Risk Evaluation and Mitigation Strategy (REMS)<sup>118,119</sup>**

A REMS program is in place for ustekinumab (Stelara) to mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS). A communication plan informs specified prescribers and dispensing pharmacists of the risks associated with ustekinumab (Stelara). In addition, a medication guide must be distributed to each patient who fills a prescription for ustekinumab (Stelara).

The FDA required a REMS program as part of the approval of tofacitinib (Xeljanz, Xeljanz XR). The goal of the Xeljanz/Xeljanz XR REMS program is to inform healthcare providers and patients about the serious risks associated with tofacitinib treatment. A medication guide should be dispensed with each tofacitinib prescription and information letters will be distributed to likely prescribers of tofacitinib.

In 2015, the FDA determined that the REMS for tocilizumab (Actemra) to ensure the benefits of the drug outweigh the potential risks was no longer necessary.

### **DRUG INTERACTIONS<sup>120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136</sup>**

Interactions relating to vaccine use is within the Warnings section above.

#### **abatacept (Orencia)**

Concurrent administration of a TNF $\alpha$ -blocker with abatacept is not recommended since combination therapy has been associated with an increased risk of serious infections with no additional efficacy over TNF $\alpha$ -blocker monotherapy. There is insufficient experience to assess the safety and efficacy of abatacept administered concurrently with anakinra; therefore, such use is not recommended.

Live vaccines should not be given concurrently with abatacept or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving abatacept. Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations.

#### **adalimumab (Humira)**

Adalimumab should not be used with anakinra, abatacept, or other TNF $\alpha$ -blockers, although it is unknown if any adverse effects would occur. Concomitant therapy may increase the potential for infections and have an impact on the development and course of malignancies. Although not specifically evaluated, patients receiving immunosuppressives along with adalimumab may be at a greater risk of developing an infection. In studies of adalimumab, many of the serious infections occurred in patients on immunosuppressive therapy.

The clearance of adalimumab was decreased by 44% after multiple doses of methotrexate. No dose adjustment for either drug is needed when methotrexate and adalimumab are used together.

Adalimumab should not be given concurrently with live vaccines.

### **anakinra (Kineret)**

In a study in which patients with active RA were treated for up to 24 weeks with concurrent anakinra and etanercept therapy, a 7% rate of serious infections was observed, which was higher than that observed with etanercept alone (0%). Two percent of patients treated concurrently with anakinra and etanercept developed neutropenia. Combination therapy with any TNF-blocking agents and anakinra is not recommended.

No data are available for anakinra and the administration of live vaccines. Concurrent administration of live vaccines is not recommended.

### **apremilast (Otezla)**

Co-administration of the strong cytochrome P450 (CYP450) enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. The use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with apremilast is not recommended.

### **canakinumab (Ilaris)**

No formal drug interaction studies have been conducted with canakinumab. However, concomitant use of canakinumab with TNF blockers should be avoided because of the potential for an increased risk of infections.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab so live vaccines should not be given concurrently with canakinumab.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation which may occur during canakinumab treatment. This may cause an interaction with CYP450 substrates and patients being treated with CYP450 enzymes should be monitored and may need to be adjusted as needed.

### **certolizumab pegol (Cimzia)**

Concurrent administration of anakinra and another TNF blocker has shown an increased risk of serious infections, an increased risk of neutropenia, and no added benefit compared to these medicinal products alone. Do not administer certolizumab pegol in combination with biological DMARDs or other TNF-blocker therapies.

Do not give live, including attenuated, vaccines concurrently with certolizumab pegol.

Interference with certain coagulation assays has been detected in patients treated with certolizumab pegol. Certolizumab pegol may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. Interference with thrombin time and prothrombin time assays has not been observed. There is no evidence that certolizumab pegol therapy has an effect on *in vivo* coagulation.

## **etanercept (Enbrel)**

Concurrent or recent exposure to myelosuppressive anti-rheumatic agents (e.g., azathioprine, cyclophosphamide, leflunomide, or methotrexate) has been associated with pancytopenia, including aplastic anemia, in some patients treated with etanercept. Etanercept is, however, commonly given in combination with methotrexate. The use of etanercept with cyclophosphamide is not recommended.

In a study of patients with Wegener's granulomatosis, the addition of etanercept to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies. Use of etanercept in patients receiving concurrent cyclophosphamide therapy is not recommended.

Patients in a clinical study who were on established therapy with sulfasalazine, to which etanercept was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either therapy alone. The clinical significance of this observation is unknown.

Live vaccines should not be given concurrently with etanercept.

Serious infections were seen in clinical studies with concurrent use of anakinra or abatacept and etanercept, with no added benefit.

## **golimumab (Simponi, Simponi Aria)**

When used in combination with abatacept (Orencia) or anakinra (Kineret), an increased risk of serious infections with no added therapeutic benefit has been observed with other TNF blockers in clinical RA studies. Therefore, use of golimumab with abatacept or anakinra is not recommended.

During chronic inflammation, the formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF $\alpha$ ). Consequently, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of golimumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted, as needed.

Live vaccines should not be given concurrently with golimumab.

## **infliximab (Remicade)**

Patients receiving immunosuppressives tend to have fewer infusion-related reactions to infliximab as compared to patients not receiving immunosuppressive therapy. In patients receiving immunosuppressant therapy with azathioprine, mercaptopurine, or methotrexate, antibody development to infliximab is lower compared to patients not receiving concurrent immunosuppression. Many serious infections during infliximab therapy have occurred in patients receiving concurrent immunosuppressives.

Rheumatoid arthritis patients who received methotrexate in combination with infliximab have higher serum concentrations of infliximab as compared to those who receive infliximab alone.

Combination therapy with any TNF-blocking agents and anakinra or abatacept is not recommended due to the potential for increased risk of infections without any increase in efficacy as seen in clinical trials with etanercept and anakinra. The use of tocilizumab in combination with biological DMARDs

such as TNF antagonists, including infliximab, should be avoided because of the possibility of increased immunosuppression and increased risk of infection.

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently.

It is recommended that all pediatric Crohn's disease patients be brought up-to-date with all vaccinations prior to initiating infliximab therapy.

It is recommended that therapeutic infectious agents (e.g., BCG in bladder cancer) not be given concurrently with infliximab.

### **ixekizumab (Taltz)**

Avoid the use of live vaccines in patients treated with ixekizumab.

During chronic inflammation, CYP450 enzyme levels may be altered due to increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF $\alpha$ , IFN). Ixekizumab could normalize the formation of CYP450 enzymes. Therefore, upon initiation or discontinuation of ixekizumab in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.

### **rilonacept (Arcalyst)**

No formal drug interaction studies have been conducted with rilonacept. However, concomitant use of rilonacept with TNF blockers should be avoided because of the potential for an increased risk of infections.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation which may occur during rilonacept treatment. This may cause an interaction with CYP450 substrates and patients being treated with CYP450 enzymes should be monitored and may need to be adjusted as needed.

### **secukinumab (Cosentyx)**

No formal drug interaction studies have been conducted with secukinumab; however, concomitant use of secukinumab with TNF blockers should be avoided because of the potential for an increased risk of infections.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-17A) during chronic inflammation which may occur during secukinumab treatment. This may cause an interaction with CYP450 substrates and patients being treated with CYP450 enzymes should be monitored and may need to have therapy adjusted.

Live vaccines should not be given concurrently with secukinumab.

### **tocilizumab (Actemra)**

Tocilizumab has not been studied in combination with biological DMARDs, such as TNF antagonists. Tocilizumab should not be administered with live vaccines.

In infection and inflammation, the cytochrome P450 enzymes are down-regulated by cytokines, including IL-6. By inhibiting IL-6 signaling in RA patients by tocilizumab, CYP450 enzyme activity may be restored to higher levels than those in the absence of tocilizumab. This may increase the metabolism of CYP450 substrates. *In vitro* studies showed that tocilizumab may change the expression of many of the CYP450 enzymes responsible for drug metabolism, including CYP 1A2, 2C9, 2D6, and 3A4. The effect of tocilizumab on CYP450 enzymes may be clinically relevant for CYP450 substrates with a narrow therapeutic index. Upon initiation or discontinuation of tocilizumab, patients being treated with medications metabolized via CYP450 systems may need to be monitored (e.g., warfarin) or drug concentration evaluated (e.g., theophylline, cyclosporine) and adjustments made, if necessary. The effect of tocilizumab may be apparent for several weeks following the last dose.

### **tofacitinib (Xeljanz, Xeljanz XR)**

Tofacitinib exposure is increased when co-administered with potent inhibitors of cytochrome P450 enzymes, CYP3A4 (e.g., ketoconazole), and with co-administration of drugs that are both moderate inhibitors of CYP3A4 and potent inhibitors of CYP2C19 (e.g., fluconazole). The dose of tofacitinib should be reduced to 5 mg once daily in patients taking these medications (**the extended-release formulation should not be used**). In contrast, potent inducers of CYP3A4 (e.g., rifampin) decrease tofacitinib exposure and concomitant use is not recommended.

There is a risk of added immunosuppression when tofacitinib is co-administered with potent immunosuppressive drugs (e.g., azathioprine, tacrolimus, cyclosporine). Combined use with potent immunosuppressives has not been studied in RA.

### **ustekinumab (Stelara)**

Patients who are receiving ustekinumab should not receive live vaccines. The safety of ustekinumab given with other immunosuppressive drugs or phototherapy has not been evaluated. CYP450 substrates should be monitored, as ustekinumab can alter the formation of CYP450 enzymes. This is especially important for agents with a narrow therapeutic effect, such as warfarin and cyclosporine.

BCG vaccines should not be given during treatment with ustekinumab or for 1 year prior to initiating treatment or 1 year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving ustekinumab because of the potential risk for shedding from the household contact and transmission to patient. Non-live vaccinations received during ustekinumab therapy may not elicit an immune response sufficient to prevent disease. Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab may decrease the protective effect of allergy immunotherapy and may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Use caution in patients receiving or who have received allergy immunotherapy and monitor for anaphylaxis.

Ustekinumab in combination with immunosuppressive agents or phototherapy has not been evaluated.

### **vedolizumab (Entyvio)**

Concomitant use of vedolizumab with natalizumab should be avoided because of the potential for increased risk of PML and other infections.

Concomitant use of vedolizumab with TNF blockers should be avoided because of the potential for increased risk of infections.

Live vaccines may be administered concurrently with vedolizumab only if the benefits outweigh the risks.

## ADVERSE EFFECTS<sup>137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153</sup>

### In Adults

Drug	Injection site/ Infusion reaction	Infection		Headache	Nausea
		Upper respiratory	Other		
Anti-TNF Biologics					
adalimumab (Humira)	20 (14)	17 (13)	serious infections 4.7/100 p/yr (2.7/100 p/yr)	12 (8)	9 (8)
certolizumab pegol (Cimzia)	reported	18-20 (13)	Total infections in Crohn’s patients 38 (30) Total Infections in RA patients 0.91/p/yr (0.72/ p/yr)	5 (with MTX; 4 with MTX alone)	nr
etanercept (Enbrel)	15-43 (6–11)	17-65 (17-30)	Total Infections: 27–81 (28–39) Serious Infections: 1.4 (0.8)	nr	nr
golimumab (Simponi)	SC: 6 (2)	SC: 16 (13)	SC – Serious Infections 5.7/100 p/yr (4.2/100 p/yr)	nr	nr
golimumab (Simponi Aria)	IV: 2 (1)	IV: 13 (12)	IV – Serious Infections 4.07/100 p/yr	nr	nr
infliximab (Remicade)	20 (10)	32 (25)	27-36 (18–25)	18 (14)	21 (20)
Other Biologic Agents					
abatacept (Orencia)	9 (6) IV: 2.5% (18/721) SC: 2.6% (19/736)	5–13	Total Infections 54 (48) Serious Infections 3 (1.9)	18 (13)	reported
anakinra (Kineret)	71 (29)	14 (17)	39 (37)	12 (9)	8 (7)
canakinumab (Ilaris)	6.8	reported	37.8	14	14
ixekizumab (Taltz)	17 (3)	14 (13)	27 (23)	nr	2 (1)
rilonacept (Arcalyst)	11 (3)	6 (1)	34 (27)	nr	4 (13)
secukinumab (Cosentyx)	nr	2.5-3.2	Total Infections: 47.5 Serious Infections: 1.2	nr	nr
tocilizumab (Actemra)	SC: 7.1–10.1 (2.4-4.1)	nr	nr	nr	nr
tocilizumab (Actemra)	IV: 7–8 (5)	5–8 (6)	Serious Infections 3.6/100 p/yr (1.5/100 p/yr)	5-7 (2-3)	nr
ustekinumab (Stelara)	1–2 ( $<1$ )	4–5 (5)	Serious Infections 0.01/ p/yr (0.02/ p/yr)	5 (3)	nr
vedolizumab (Entyvio)	4 (3)	7 (6)	0.85/p/yr (0.7/p/yr)	12 (11)	9 (8)

nr = not reported, na = not applicable, p/yr = patient-year, MTX = methotrexate

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive. Incidences for placebo are indicated in parentheses.

### Adverse Effects In Adults (continued)

Drug	Injection site/ Infusion reaction	Infection		Headache	Nausea
		Upper respiratory	Other		
Non-biologic Agents					
apremilast (Otezla)	na	0.6 (0.6)	nr	4.8 (1.8)	7.4 (1.4)
tofacitinib (Xeljanz, Xeljanz XR)	na	4.5 (3.3)	Serious Infections 1.7/100 p/yr (0.5/100 p/yr) 20 (18)	4.3 (2.1)	reported

nr = not reported, na = not applicable, p/yr = patient-year, MTX = methotrexate

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive. Incidences for placebo are indicated in parentheses.

In placebo-controlled studies, 8% of patients receiving anakinra had decreases in neutrophil counts of at least 1 World Health Organization (WHO) toxicity grade compared with 2% of patients in the placebo control group. Six (0.3%) of the anakinra-treated patients experienced neutropenia. Neutrophil counts should be obtained prior to initiating anakinra, while on therapy, monthly for 3 months, and thereafter quarterly for a period up to 1 year.

To investigate whether TNF- $\alpha$  inhibitors, together as a class, or separately as either monoclonal anti-TNF- $\alpha$  antibodies (adalimumab, infliximab) or a fusion protein (etanercept), are related to higher rates of herpes zoster in patients with RA, patients were enrolled in a prospective cohort.<sup>154</sup> Patients were enrolled at the initiation of treatment with etanercept, adalimumab, infliximab, or anakinra, or when they changed conventional DMARD treatment. Treatment, clinical status, and adverse events were assessed by rheumatologists at fixed points during follow-up. Among the 5,040 patients receiving TNF blockers or conventional DMARDs, 86 episodes of herpes zoster occurred in 82 patients. Thirty-nine of these occurrences could be attributed to treatment with adalimumab or infliximab, 23 to etanercept, and 24 to conventional DMARDs. Adjusted for age, rheumatoid arthritis severity, and glucocorticoids use, a significantly increased risk was observed for treatment with the monoclonal antibodies. Treatment with monoclonal anti-TNF- $\alpha$  inhibitors (adalimumab, infliximab) may be associated with increased risk of herpes zoster, but further study is required.

## In Pediatric Patients

Drug	Injection Site/ Infusion Reaction	Infection
<b>Anti-TNF Biologics</b>		
adalimumab (Humira)	16	45
etanercept (Enbrel)	reported	reported
infliximab (Remicade)	18	65 to 68
<b>Other Biologic Agents</b>		
abatacept (Orencia)	2 to 4	36
anakinra (Kineret)	16	Total infections 2.3 infections/patient-year in first 6 months of therapy 1.7 infections/patient-year after the first 6 months of therapy
tocilizumab (Actemra)	16 – SJIA 20.2 – PJIA	Total Infections 163.7/100 patient years – SJIA 345/100 patient-years – PJIA (287/100 patient-years)

nr = not reported

PJIA = polyarticular juvenile idiopathic arthritis; SJIA = systemic juvenile idiopathic arthritis

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive.

## Monitoring

In patients receiving tofacitinib (Xeljanz, Xeljanz XR), lymphocyte counts should be obtained at baseline and every 3 months thereafter. Neutrophil counts should be obtained at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. Hemoglobin should be checked at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. Routine liver tests should also be performed along with lipid assessments approximately 4 to 8 weeks following initiation of therapy.

Tocilizumab (Actemra) requires monitoring of neutrophils, platelets, and liver enzymes (ALT and AST) after 4 to 8 weeks and every 3 months thereafter. Therapy with tocilizumab may be withheld, dose reduced, or maintain current therapy depending on the results. Lipid parameters should be measured after 4 to 8 weeks of tocilizumab therapy and then every 6 months. Patients should be managed according to the latest lipid guidelines for hyperlipidemia. Patients with an absolute neutrophil count (ANC) below 2,000/mm<sup>3</sup>, platelet count below 100,000/mm<sup>3</sup>, or ALT or AST above 1.5 times the upper limit of normal should not initiate therapy with tocilizumab.

## SPECIAL POPULATIONS<sup>155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171</sup>

## Pediatrics

In November 2009, the boxed warning for the TNF blockers was updated to include the risk of malignancies, some fatal, associated with the use of TNF blockers in children and young adults. Approximately half of the cases were lymphoma. Some malignancies were rare and usually associated with immunosuppression and not typically observed in children and adolescents.

## **abatacept (Orencia)**

Abatacept (Orencia) is indicated for reducing signs and symptoms of JIA in children over 6 years of age. Children should be brought up-to-date with all immunizations according to current immunization guidelines prior to initiating therapy with abatacept.

A double-blind, randomized controlled withdrawal trial enrolled 190 patients ages 6 to 17 years with active JIA in at least 5 active joints with an inadequate response or intolerance to at least 1 DMARD.<sup>172</sup> All 190 patients were given 10 mg/kg of abatacept intravenously in the open-label period of four months. Of the 170 patients who completed the lead-in course, 47 did not respond to the treatment according to predefined American College of Rheumatology (ACR) pediatric criteria and were excluded. An ACR 30 response requires a patient to have a 30% reduction in the number of swollen and tender joints, and a reduction of 30% in 3 of the following 5 parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate. Of the patients who responded to abatacept, 60 were randomly assigned to receive abatacept 10 mg/kg every 28 days for 6 months, or until a flare of the arthritis, and 62 were randomly assigned to receive placebo at the same dose and timing. The primary endpoint was time to flare of arthritis. Flare was defined as worsening of 30% or more in at least 3 of 6 core variables, with at least 30% improvement in no more than 1 variable. Flares of arthritis occurred in 33 of 62 (53%) patients who were given placebo and 12 of 60 (20%) abatacept patients during the double-blind treatment ( $p=0.0003$ ). Median time to flare of arthritis was 6 months for patients given placebo; insufficient events had occurred in the abatacept group for median time to flare to be assessed ( $p=0.0002$ ). The risk of flare in patients who continued abatacept was less than a third of that for controls during that double-blind period (hazard ratio, 0.31; 95% CI, 0.16 to 0.95). During the double-blind period, the frequency of adverse events did not differ in the 2 treatment groups. Adverse events were recorded in 37 abatacept recipients (62%) and 34 (55%) placebo recipients ( $p=0.47$ ); only 2 serious adverse events were reported, both in controls ( $p=0.5$ ). The manufacturer of abatacept funded the study. Of the 190 enrolled patients, 153 patients entered the long-term extension phase. By day 589 ( $\geq 21$  months), the percentage of patients reaching various ACR criteria in the double-blind and long-term extension phases were the following: ACR Pedi 30 (90%), ACR Pedi 50 (88%), ACR Pedi 70 (75%), ACR Pedi 90 (57%), and ACR Pedi 100 (39%).<sup>173</sup> Similar response rates were observed by day 589 among patients previously treated with placebo. Among patients who had not achieved an ACR Pedi 30 response at the end of the open-label lead-in phase and who proceeded directly into the long term extension phase, 73%, 64%, 46%, 18%, and 5% achieved ACR Pedi 30, Pedi 50, Pedi 70, Pedi 90, and Pedi 100 responses, respectively, by day 589. Tuberculosis and malignancies were not reported during the long term extension phase.

## **adalimumab (Humira)**

Adalimumab (Humira) is indicated for reducing signs and symptoms of JIA in children 4 years of age or older. Children should be brought up-to-date with all immunizations according to current immunization guidelines prior to initiating therapy with adalimumab. Patients on adalimumab may receive concurrent vaccination except live vaccines.

A randomized, double-blind, placebo-controlled, multi-center, medication-withdrawal study with a 16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase enrolled patients ages 4 to 17 years with active JIA.<sup>174</sup> Patients who had previously received treatment with NSAIDs underwent stratification according to methotrexate use. Patients received

adalimumab 24 mg/m<sup>2</sup> of body surface area (maximum dose 40 mg) subcutaneously every other week for 16 weeks. Patients with an ACR Pedi 30 response at week 16 were randomized to adalimumab or placebo every other week in a double-blind manner for up to 32 weeks. More patients on methotrexate (94%, 80/85 patients) achieved ACR Pedi 30 response at week 16 compared to those not on methotrexate (74%, 64/86 patients). Patients not receiving methotrexate, disease flares occurred in 43% of adalimumab-treated patients and 71% of placebo-treated patients (p=0.03). Among patients receiving methotrexate, flares occurred in 37% adalimumab-treated patients and 65% of placebo-treated patients (p=0.02). At 48 weeks, the percentages of patients treated with methotrexate who had ACR Pedi 30, 50, 70, or 90 responses were significantly greater for those receiving adalimumab than for those receiving placebo; the differences between patients not treated with methotrexate who received adalimumab and those who received placebo were not significant. The most frequently reported adverse events were infections and injection site reactions.

### **anakinra (Kineret)**

Anakinra (Kineret) is approved for use in pediatric patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), a rare periodic fever syndrome which causes uncontrolled inflammation in multiple parts of the body beginning in the newborn period. The pre-filled syringe does not permit accurate dosing lower than 20 mg. Anakinra has been studied in pediatric patients with JIA.<sup>175</sup>

In a long-term, open-label and uncontrolled study, 43 NOMID patients 0.7 to 46 years of age were treated for up to 60 months. Patients were given an initial dose of anakinra 1-2.4 mg/kg, which was titrated by 0.5 to 1 mg/kg increments to control signs and symptoms of disease to a maximum of 10 mg/kg daily. The actual maximum dose studied was 7.6 mg/kg/day. The average maintenance dose was 3 to 4 mg/kg daily. The dose was given once daily, in general, but, for some patients, the dose was split into twice daily administrations for better control of disease activity. NOMID symptoms were assessed with a disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache. Improvements occurred in all individual disease symptoms comprising the DSSS and the estimated changes from baseline in DSSS were -3.5 (95% CI, -3.7 to -3.3) which was seen as early as month 3 and continued through month 60. In addition, improvements in serum markers of inflammation (e.g., serum amyloid A [SAA], high-sensitivity C-reactive protein [hsCRP], and erythrocyte sedimentation rate [ESR]) were also evident. For 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of anakinra therapy. Upon withdrawal of treatment, the median time until disease flare criteria were met was 5 days.

### **canakinumab (Ilaris)**

The trials assessing safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndromes (CAPS) included a total of 23 pediatric patients with an age range from 4 years to 17 years. The majority of patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g., SAA and C-reactive protein [CRP]). Overall, the efficacy and safety of canakinumab in pediatric and adult patients were comparable. The safety and effectiveness of canakinumab in CAPS patients under 4 years of age have not been established.

## **etanercept (Enbrel)**

Etanercept (Enbrel) is indicated for the treatment of JIA in children older than 2 years of age. Limited data on safety and effectiveness are available for etanercept in the management of moderate to severe chronic plaque psoriasis in children and adolescents.<sup>176</sup> Children should be brought up-to-date with all immunizations according to current immunization guidelines prior to initiating therapy with etanercept. Patients with a significant exposure to varicella virus should temporarily discontinue etanercept and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

A long-term, open-label extension study evaluated etanercept in 58 patients with JIA for up to 8 years.<sup>177</sup> A total of 42 of the 58 patients (72%) entered the fourth year of continuous etanercept treatment, and 26 patients (45%) entered the eighth year. Efficacy endpoints included the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), 50, 70, 90, and 100 criteria for improvement. The degree of disability in Health Assessment Questionnaire (HAQ) score was also evaluated. An ACR Pedi 70 response or higher was achieved by 100% of patients (n=11) with 8 years of data and by 61% of patients (28 of 46) according to the last observation carried forward data. The overall rate of adverse events (0.12 per patient-year) did not increase with long-term exposure to etanercept.

## **infliximab (Remicade)**

Infliximab (Remicade) is indicated in children (>6 years) for the treatment of Crohn's Disease and for the treatment of ulcerative colitis. Safety and effectiveness data for infliximab in children for the management of psoriatic arthritis or plaque psoriasis are not available. Infliximab has been studied in children with juvenile rheumatoid arthritis (JRA); however, efficacy was not established in a double-blind, 14-week study with children ages 4 to 17 years.

The REACH study evaluated the safety and efficacy of infliximab in children with moderately to severely active Crohn's disease.<sup>178</sup> Patients (n=112) received infliximab 5 mg/kg at weeks 0, 2, and 6. Patients responding to treatment at week 10 were randomized to infliximab 5 mg/kg every 8 or 12 weeks through week 46. A concurrent immunomodulator was required. Clinical response (decrease from baseline in the pediatric Crohn's disease activity index (PCDAI) score  $\geq 15$  points; total score  $\leq 30$ ) and clinical remission (PCDAI score  $\leq 10$  points) were evaluated at weeks 10, 30, and 54. At week 10, 88.4% patients responded to infliximab (95% CI, 82.5% to 94.3%) and 58.9% patients achieved clinical remission (95% CI, 49.8% to 68%). At week 54, 63.5% and 55.8% patients receiving infliximab every 8 weeks did not require dose adjustment and were in clinical response and clinical remission, respectively, compared with 33.3% and 23.5% patients receiving treatment every 12 weeks (p=0.002 and p<0.001, respectively).

## **rilonacept (Arcalyst)**

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with rilonacept at a weekly, subcutaneous dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24 weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g., SAA and CRP). The adverse events included injection site reactions and upper respiratory symptoms as were commonly seen in the adult subjects. Safety and effectiveness in pediatric patients below the age of 12 have not been established.

## **tocilizumab (Actemra)**

Tocilizumab is indicated for polyarticular and systemic JIA in children ages 2 years and older.

Tocilizumab was assessed in a 3-part study in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), who had an inadequate response to methotrexate or inability to tolerate methotrexate.<sup>179,180</sup> Patients had at least 6 months of active disease, with at least 5 joints with active arthritis and/or at least 3 active joints having limitation of motion. JIA subtypes at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of methotrexate was permitted but DMARDs, other than methotrexate, or other biologics (e.g., TNF antagonists or T-cell costimulation modulator) were not permitted. Part 1 of the study was a 16-week active tocilizumab treatment lead-in period (n=188), part 2, a 24-week randomized double-blind placebo-controlled withdrawal period, and part 3, a 64-week open-label period. Patients weighing 30 kg or more received tocilizumab 8 mg/kg IV once every 4 weeks. Patients weighing less than 30 kg received either tocilizumab 8 mg/kg or 10 mg/kg IV in a randomized 1:1 ratio every 4 weeks. At the end of part 1, 91% of patients taking background methotrexate in addition to tocilizumab and 83% of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 and entered the blinded withdrawal period (part 2). In part 2, patients (ITT, n=163) were randomized to tocilizumab (same dose as in Part 1) or placebo in a 1:1 ratio that was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in part II until week 40 or until they showed JIA ACR 30 flare criteria (relative to week 16) and the subject qualified for escape. The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to week 16. Tocilizumab-treated patients experienced fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; with an adjusted difference in proportions of -21%; 95% CI, -35 to -8%).

The efficacy of tocilizumab was assessed in active systemic JIA in a 12-week randomized, double-blind, placebo-controlled, parallel group study in children aged 2 and older.<sup>181</sup> One hundred and twelve patients, treated with or without methotrexate, were randomized 2:1 to receive to tocilizumab (n=75) or placebo (n=37). Every 2 weeks, patients less than 30 kg received tocilizumab or placebo infusions at 12 mg/kg and those above 30 kg received tocilizumab or placebo infusions at 8 mg/kg. The primary endpoint was the proportion of patients at week 12 with at least a 30% improvement in American College of Rheumatology Juvenile Idiopathic Arthritis (JIA ACR 30) in 3 of 6 core outcome variables compared to baseline and absence of fever during the preceding 7 days. After 6 weeks, patients who achieved a JIA ACR 70 response could begin corticosteroid tapering. The JIA ACR 30 response rates with absence of fever at week 12 were 85% for tocilizumab and 24% for placebo, with a weighted difference between the tocilizumab and placebo response rates stratified for weight, disease duration, background oral corticosteroid dose, and background methotrexate use of 62% (95% CI, 45% to 78%).

Efficacy and safety of tocilizumab in patients with systemic JIA were evaluated in a randomized, double-blind, placebo-controlled, phase 3 study with 56 Japanese children with JIA ages 2 to 19 years.<sup>182</sup> Patients had disease refractory to conventional treatment. Patients were given tocilizumab 8 mg/kg every 2 weeks for 6 weeks in an open-label manner. Patients with ACR Pedi 30 response and C-reactive protein (CRP) of less than 5 mg/L were randomized in a double-blind manner to placebo or continuation of tocilizumab for 12 weeks or until withdrawal for rescue medication. At the end of the open-label lead-in phase, ACR Pedi 30, 50, and 70 responses were achieved by 51 (91%), 48 (86%), and 38 (68%) patients, respectively. A total of 43 patients continued to the double-blind phase. In the tocilizumab group, 80% (n=16/20) maintained ACR Pedi 30 response and CRP less than 15 mg/L compared to 17% (n=4/23) of patients receiving placebo. In the open-label extension phase to 48

weeks, ACR Pedi 30, 50, and 70 responses were achieved by 47 (98%), 45 (94%), and 43 (90%) of 48 patients, respectively. Serious adverse events were anaphylactoid reaction, gastrointestinal hemorrhage, bronchitis, and gastroenteritis.

Safety and effectiveness of apremilast (Otezla), certolizumab pegol (Cimzia), golimumab (Simponi), ixekizumab (Taltz), secukinumab (Cosentyx), tofacitinib (Xeljanz, Xeljanz XR), ustekinumab (Stelara), and vedolizumab (Enytvio) in pediatric patients have not been established.

Inhibition of TNF $\alpha$  during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

## Pregnancy

Adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab are Pregnancy Category B. Abatacept, apremilast, canakinumab, rilonacept, tocilizumab, tofacitinib, and vedolizumab are Pregnancy Category C. There are no available human data on ixekizumab (Taltz) use in pregnant women to inform users of a drug-associated risk.

A meta-analysis of pregnancy outcomes in women using anti-TNF agents for inflammatory bowel disease (CD or UC) demonstrated no increase in occurrence of adverse pregnancy outcomes compared to controls, with the exception of a decrease in gestational age of newborns in exposed mothers in 1 trial.<sup>183</sup>

## Hepatic/Renal Impairment

Anakinra is substantially excreted by the kidneys. Consider every other day administration in patients with severe renal insufficiency or end stage renal disease (creatinine clearance [CrCL] < 30 mL/min).

The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment. No dose adjustment is required in patients with mild to moderate renal impairment.

Tofacitinib dose should not exceed 5 mg once daily as the immediate-release formulation in patients with moderate hepatic impairment. Tofacitinib is not recommended in severe hepatic impairment. Tofacitinib dose should not exceed 5 mg once daily as the immediate-release formulation in patients with moderate or severe renal impairment. The extended-release formulation should not be used in these populations.

## Other

There have been reports of hypoglycemia following initiation of etanercept (Enbrel) therapy in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

## DOSAGES<sup>184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200</sup>

Drug	Dose	Availability						
Anti-TNF Biologics								
adalimumab (Humira)	<p><b>RA, PsA, and AS:</b> 40 mg SC every other week; methotrexate, glucocorticoids, salicylates, NSAIDs, analgesics, or other DMARDs may be continued</p> <p>In RA, some patients not taking methotrexate may benefit from increasing the dosing frequency to 40 mg every week</p> <p><b>Plaque psoriasis and uveitis:</b> 80 mg SC initially (Day 1) followed by 40 mg one week later (Day 8) then 40 mg every other week starting on Day 22</p> <p><b>Crohn's disease:</b> 160 mg once followed by 80 mg at week 2 (Day 15), then 40 mg every other week beginning at week 4 (Day 29)</p> <p>The initial dose of 160 mg may be given as 4 injections of 40 mg on 1 day or given as 80 mg given on 2 consecutive days</p> <p><b>UC:</b> Initial dose: 160 mg (four 40 mg injections in 1 day [Day 1]) or two 40 mg injections per day for 2 consecutive days; these are followed by a second dose of 80 mg 2 weeks later (Day 15)</p> <p>Maintenance dose: 2 weeks later (Day 29), begin 40 mg every other week; only continue in patients with UC who have evidence of clinical remission by 8 weeks (Day 57) of therapy</p> <p><b>JIA:</b> (ages 4 to 17 years):</p> <table><tr><th>Body weight</th><th>Dose</th></tr><tr><td>15 kg to &lt; 30 kg</td><td>20 mg every other week</td></tr><tr><td>≥ 30 kg</td><td>40 mg every other week</td></tr></table> <p><b>HS:</b> Initial dose: 160 mg (four 40 mg injections in 1 day [Day 1]) or two 40 mg injections per day for 2 consecutive days; these are followed by a second dose of 80 mg 2 weeks later (Day 15)</p> <p>Maintenance dose: 2 weeks later (Day 29), begin 40 mg weekly</p>	Body weight	Dose	15 kg to < 30 kg	20 mg every other week	≥ 30 kg	40 mg every other week	<p>Prefilled syringes: 10 mg/0.2 mL, 20 mg/0.4 mL, 40 mg/0.8 mL</p> <p>Single-use pen: 40 mg/0.8 mL</p> <p>Psoriasis/Uveitis Starter Package: 4 x 40 mg prefilled pens</p> <p>Pediatric Crohn's Disease Starter Package: 6 x 40 mg prefilled pens; 3 x 40 mg prefilled syringe</p> <p>Crohn's Disease/ Ulcerative Colitis/ Hidradenitis Suppurativa Starter Package: 6 x 40 mg prefilled pens</p>
Body weight	Dose							
15 kg to < 30 kg	20 mg every other week							
≥ 30 kg	40 mg every other week							
certolizumab pegol (Cimzia)	<p><b>Crohn's disease:</b> 400 mg SC initially (given as 2 SC injections of 200 mg) and at weeks 2 and 4</p> <p>In patients who obtain a clinical response, the recommended maintenance dose is 400 mg SC every 4 weeks</p> <p><b>RA:</b> 400 mg SC initially (given as 2 SC injections of 200 mg) and at weeks 2 and 4, followed by 200 mg every 2 weeks</p> <p>For maintenance dosing, 400 mg every four weeks may be considered</p> <p><b>PsA and AS:</b> 400 mg (given as 2 SC injections of 200 mg) initially and at weeks 2 and 4, followed by 200 SC mg every 2 weeks or 400 mg SC every 4 weeks</p>	<p>Vial: 200 mg lyophilized powder for reconstitution with 1 mL diluent</p> <p>Prefilled syringe: 200 mg/mL</p> <p>400 mg kit: 2 x 200 mg vials</p>						
etanercept (Enbrel)	<p><b>RA, PsA AS:</b> 50 mg SC once weekly; methotrexate, glucocorticoids, salicylates, NSAIDs or analgesics may be continued</p> <p><b>Plaque psoriasis:</b> 50 mg SC twice weekly for 3 months followed by 50 mg weekly</p> <p><b>JIA:</b> Patients weighing ≥ 63 kg: 50 mg SC given once weekly; patients weighing &lt; 63 kg: 8 mg/kg weekly with a maximum of 50 mg per week, Glucocorticoids, NSAIDS, or analgesics may be continued:</p> <p>Higher doses of etanercept have not been studied in the pediatric population</p>	<p>Prefilled syringe: 25 mg/0.5 mL, 50 mg/1 mL</p> <p>Prefilled SureClick™ autoinjector: 50 mg/1 mL</p> <p>Multiuise vial: 25 mg with 1 mL diluent</p>						

## Dosages (continued)

Drug	Dose	Availability
<b>Anti-TNF Biologics (continued)</b>		
golimumab (Simponi, Simponi Aria)	<p><b>RA, PsA, AS:</b> SC injection 50 mg SC once monthly; For RA, give in combination with methotrexate For PsA or AS, may be given with or without methotrexate or other non-biologic DMARDs Corticosteroids, non-biologic DMARDs, and/or NSAIDs may be continued</p> <p><b>UC:</b> SC injection 200 mg SC at week 0, followed by 100 mg SC at week 2 and then 100 mg SC every 4 weeks</p> <p><b>RA:</b> IV infusion (Simponi Aria) 2 mg/kg as an IV infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter</p>	<p>Prefilled syringe for subcutaneous injection: 50 mg/0.5 mL 100 mg/1 mL</p> <p>SmartJect® autoinjector* for subcutaneous injection: 50 mg/0.5mL 100 mg/1 mL Vials</p> <p>Solution for IV infusion (Simponi Aria): 50 mg/4 mL(dilute before administration)</p>
infliximab (Remicade)	<p><b>RA:</b> 3 mg/kg IV infusion, repeated at 2 and 6 weeks, then every 8 weeks; for patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks; use methotrexate in combination</p> <p><b>AS:</b> 5 mg/kg IV infusion at 0, 2, and 6 weeks, then every 6 weeks</p> <p><b>Plaque psoriasis, PsA:</b> 5 mg/kg IV infusion at 0, 2, and 6 weeks, then every 8 weeks thereafter May be given with or without methotrexate for PsA</p> <p><b>Crohn's Disease (adults):</b> 5 mg/kg IV infusion given at 0, 2, and 6 weeks, then every 8 weeks; for patients who respond and then lose their response, consider increasing to 10 mg/kg</p> <p><b>Crohn's Disease (pediatrics):</b> 5 mg/kg IV infusion at 0, 2, and 6 weeks, then every 8 weeks</p> <p><b>Ulcerative Colitis (adults and pediatrics):</b> 5 mg/kg IV infusion at 0, 2, and 6 weeks, then every 8 weeks</p>	<p>Single dose vial: 100 mg/20 mL; given as 2-hour infusion</p>

\* The SmartJect autoinjector has specific instructions. Patients are instructed not to use the SmartJect autoinjector without training from a health care professional.

## Dosages (continued)

Drug	Dose	Availability								
Other Biologic Agents										
abatacept (Orencia)	<p><b>RA:</b> IV infusion: IV dose based on body weight given over 30 minutes at 0, 2, and 4 weeks, then every 4 weeks thereafter</p> <table><tr><th>Body weight</th><th>IV Dose</th></tr><tr><td>&lt; 60 kg</td><td>500 mg</td></tr><tr><td>60-100 kg</td><td>750 mg</td></tr><tr><td>&gt; 100 kg</td><td>1,000 mg</td></tr></table> <p><b>RA:</b> subcutaneous injection Following a single IV loading dose, the first dose of 125 mg SC should be given within 1 day; 125 mg SC is given weekly thereafter SC therapy may be initiated without the IV loading dose; If transitioning from IV therapy to SC, the first SC dose may be given instead of the next IV dose <b>JIA:</b> Pediatric patients &lt; 75 kg receive 10 mg/kg IV based on the patient’s body weight; pediatric patients weighing &gt; 75 kg should be administered abatacept at the adult dose, not to exceed 1,000 mg</p>	Body weight	IV Dose	< 60 kg	500 mg	60-100 kg	750 mg	> 100 kg	1,000 mg	Single-dose vial (SDV): 250 mg/15 mL Prefilled syringe: 125 mg/mL for subcutaneous injection Prefilled ClickJect™ autoinjector: 125 mg/mL for subcutaneous injection
Body weight	IV Dose									
< 60 kg	500 mg									
60-100 kg	750 mg									
> 100 kg	1,000 mg									
anakinra (Kineret)	<p><b>RA:</b> 100 mg SC daily Consider 100 mg every other day for RA patients who have severe renal insufficiency or end stage renal disease (creatinine clearance &lt; 30 mL/min) <b>CAPS (NOMID):</b> initiate at 1–2 mg/kg daily; adjust in increments of 0.5–1 mg/kg to a maximum of 8 mg/kg to control active inflammation Dose may be divided into twice daily administrations</p>	Prefilled syringe: 100 mg/0.67 mL Graduated syringe allows for doses between 20 and 100 mg								
canakinumab (Ilaris)	<p><b>CAPS:</b> 150 mg SC for patients with body weight greater than 40 kg 2 mg/kg SC for patients with body weight ≥15 kg and ≤40 kg 3 mg/kg SC for patients 15 to 40 kg with an inadequate response All CAPS doses should be administered every 8 weeks <b>SJIA:</b> 4 mg/kg SC for patients with body weight ≥7.5 kg All SJIA doses should be administered every 4 weeks</p>	Vial: 180 mg single use vial reconstituted to 150 mg/mL								
ixekizumab (Taltz)	<p><b>PsA:</b> 160 mg (two 80 mg injections) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks thereafter; self-administered in the thigh or abdomen or administered by a caregiver in the back of the arm†</p>	Prefilled syringe: 80 mg/mL Prefilled auto-injector: 80 mg/mL								
rilonacept (Arcalyst)	<p><b>CAPS:</b> Adults: Loading dose: 320 mg SC (2 doses at different sites)</p> <ul style="list-style-type: none"><li>Maintenance dose: 160 mg SC weekly</li><li>Pediatrics (12 to 17 years): Loading dose: 4.4 mg/kg SC</li><li>Maintenance dose: 2.2 mg/kg SC weekly</li></ul>	Vial: 220 mg single use vial								

†Patients may self-inject after receiving training in the proper SC injection technique using the autoinjector or prefilled syringe.

## Dosages (continued)

Drug	Dose	Availability
<b>Other Biologic Agents (continued)</b>		
secukinumab (Cosentyx)	<p><b>Psoriasis:</b> 300 mg SC at 0, 1, 2, 3, and 4 weeks followed by 300 mg every 4 weeks For some patients, a dose of 150 mg may be acceptable in lieu of 300 mg</p> <p><b>Psoriatic arthritis:</b> 150 mg SC at 0, 1, 2, 3, and 4 weeks, followed by 150 mg SC every 4 weeks (with loading dose) or 150 mg SC every 4 weeks (without loading dose) For some patients, a dose of 300 mg may be used if response to 150 mg is insufficient Patients with both psoriasis and psoriatic arthritis should receive the psoriasis dosing</p> <p><b>AS:</b> 150 mg SC at 0, 1, 2, 3, and 4 weeks followed by 150 mg SC every 4 weeks (with loading dose) or 150 mg SC every 4 weeks (without loading dose)</p>	<p>Single-use Sensoready® pen: 150 mg/mL</p> <p>Single-use prefilled syringe: 150 mg/mL solution</p>
tocilizumab (Actemra)	<p><b>RA (adults):</b> IV infusion starting dose 4 mg/kg 1-hour IV infusion every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response; do not exceed 800 mg per infusion</p> <p><b>RA (adults):</b> SC injection In patients &lt; 100 kg starting dose is 162 mg SC every other week, followed by an increase to every week based on clinical response In patients ≥ 100 kg, 162 mg SC every week When transitioning from IV to SC, administer the first SC dose instead of the next scheduled IV dose May be used as monotherapy or concomitantly with methotrexate or other DMARDs</p> <p><b>Polyarticular JIA (ages 2 to 17 years):</b> For patients weighing &lt; 30 kg: 10 mg/kg IV over 1 hour every 4 weeks For patients weighing &gt; 30 kg: 8 mg/kg IV over 1 hour every 4 weeks May give alone or in combination with methotrexate</p> <p><b>Systemic JIA (ages 2 to 17 years):</b> For patients weighing less than 30 kg: 12 mg/kg IV over 1 hour every 2 weeks For patients weighing &gt; 30 kg: 8 mg/kg IV over 1 hour every 2 weeks May give alone or in combination with methotrexate SC administration is not approved for PJIA or SJIA Dose modifications: see prescribing information for details on dose modifications for liver enzyme elevation, low absolute neutrophil count (ANC), low platelet count, or infection</p>	<p>Single dose vials: 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL</p> <p>Prefilled syringe: 162 mg/0.9 mL<sup>‡</sup></p>

<sup>‡</sup> SC tocilizumab can be self-administered after proper training by a healthcare professional.

## Dosages (continued)

Drug	Dose	Availability
<b>Other Biologic Agents (continued)</b>		
ustekinumab (Stelara)	<p><b>Psoriasis:</b> Dose is based on body weight; given under supervision by a physician and administered by a health care professional or by self administration after training, if deemed appropriate</p> <p>For patients weighing ≤ 100 kg, the initial recommended dose is 45 mg SC followed by another dose 4 weeks later, followed by 45 mg SC every 12 weeks</p> <p>For patients weighing ≥ 100 kg, the recommended dose is 90 mg SC initially, followed by another dose 4 weeks later, followed by 90 mg SC every 12 weeks</p> <p><b>PsA:</b> 45 mg SC followed by another dose 4 weeks later, followed by 45 mg every 12 weeks, for patients with co-existent moderate-to-severe plaque psoriasis weighing &gt; 100 kg, the recommended dose is 90 mg SC initially, followed by another dose 4 weeks later, followed by 90 mg SC every 12 weeks</p>	<p>Single dose vials: 45 mg/0.5 mL, 90 mg/1 mL</p> <p>Prefilled syringe: 45 mg/0.5 mL, 90 mg/1 mL</p>
vedolizumab (Entyvio)	<p><b>Crohn's Disease and Ulcerative Colitis:</b> 300 mg administered by a healthcare professional by IV infusion at weeks 0, 2, and 6 and then every 8 weeks thereafter</p>	Single use vial: 300 mg
<b>Non-biologic Agents</b>		
apremilast (Otezla)	<p><b>Plaque psoriasis and PsA:</b> Initial titration: Day 1: 10 mg in morning, Day 2: 10 mg in morning and 10 mg in evening, Day 3: 10 mg in morning and 20 mg in evening, Day 4: 20 mg in morning and 20 mg in evening, Day 5: 20 mg in morning and 30 mg in evening</p> <p>Maintenance Dose: 30 mg twice daily</p>	<p>Tablet: 30 mg</p> <p>Starter Pack (28 day): 10, 20, and 30 mg tablets</p>
tofacitinib (Xeljanz, Xeljanz XR)	<p><b>RA:</b> 5 mg immediate-release (IR) orally twice daily or 11 mg extended-release (ER) once daily with or without food</p> <p>May be used as monotherapy or in combination with methotrexate or other nonbiologic (DMARDs)</p> <p>No dose adjustments or tapering/titration is required when switching from the IR to the ER formulation; the ER dose may be started once daily after discontinuation of the IR formulation when the next dose is due</p> <p>Dose modifications: Dose interruption is recommended for management of lymphopenia, neutropenia, and anemia with specific details in the prescribing information; dosage should be reduced to 5 mg once daily in patients with moderate or severe renal insufficiency, moderate hepatic impairment, or those receiving potent or multiple moderate inhibitors of CYP3A4; the ER formulation should not be used when dose modifications are required.</p>	<p>Tablet: 5 mg</p> <p>Extended-release tablet: 11 mg</p>

## CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined

to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

## Ankylosing Spondylitis

### *adalimumab (Humira)*

A multicenter, randomized (2:1 ratio), double-blind, placebo-controlled study assessed the safety and efficacy of adalimumab 40 mg every other week in 315 patients with active ankylosing spondylitis.<sup>201</sup> Adalimumab or placebo was given for 24 weeks. At 12 weeks, the Assessment in Ankylosing Spondylitis International Working Group criteria with 20% improvement (ASAS20) was achieved in 58.2 and 20.6% for the adalimumab and placebo groups, respectively ( $p<0.001$ ). The domains within the ASAS 20 response criteria include measures of physical function, pain, inflammation (assessed by duration of morning stiffness), and patient's global assessment. Improvement is defined as a 20% improvement and  $\geq 10$  units of absolute change (on a 0 to 100 scale) in each of 3 domains, with no worsening of a similar amount in the fourth domain.<sup>202</sup> At week 12, more patients in the adalimumab group (45.2%) had at least 50% improvement in the Bath ankylosing spondylitis disease activity index (BASDAI) compared to the placebo group (15.9%;  $p<0.001$ ). Adalimumab-treated patients reported more adverse events (75% versus 59.8%;  $p<0.05$ ). The incidence of infections was similar in both groups. A total of 255 patients (82%) entered the 2-year open-label extension study and continued on adalimumab 40 mg every other week.<sup>203</sup> ASAS responses were maintained; 64.5% were ASAS20 responders, and 50.6% were ASAS40 responders.

A closer evaluation of adalimumab on pain, fatigue, and morning stiffness was performed during the ATLAS (Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis) study.<sup>204</sup> Pain and fatigue were assessed by the scores of the Medical Outcomes Study Short Form-36 (SF-36) Health Survey (SF-36) and also by total back pain and nocturnal pain using visual analog scales. Fatigue and morning stiffness were also assessed by portions of the BASDAI. At week 12, adalimumab-treated patients experienced significant improvement compared with placebo-treated patients in the SF-36 bodily pain score ( $p<0.001$ ), total back pain score ( $p<0.001$ ), nocturnal pain score ( $p<0.001$ ), fatigue ( $p<0.01$ ), and morning stiffness ( $p<0.001$ ). Treatment effects were maintained through 24-weeks of treatment. Adalimumab significantly improved patient-reported physical function and health-related quality of life in the 3-year open-label extension of the ATLAS study.<sup>205</sup>

In a randomized, multicenter, double-blind, placebo-controlled study, the efficacy of adalimumab and placebo were compared for reducing spinal and sacroiliac joint inflammation, as measured by magnetic resonance imaging (MRI), in 82 patients with ankylosing spondylitis.<sup>206</sup> Patients received adalimumab 40 mg or placebo every other week during an initial 24-week double-blind period. MRIs of both the spine and sacroiliac (SI) joints were obtained at baseline, week 12, and week 52. Spinal and SI joint inflammation were measured using the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index. The spine SPARCC score in placebo-treated patients increased by a mean of 9.4% from baseline, compared with a mean decrease of 53.6% in adalimumab-treated patients ( $p<0.001$ ). The SI joint SPARCC score decreased by a mean of 12.7% from baseline in placebo-treated patients and by 52.9% in adalimumab-treated patients ( $p=0.017$ ). The response in adalimumab-treated patients was maintained at week 52. Placebo-treated patients were switched to open-label adalimumab treatment at week 24 and experienced similar reductions in spinal and SI joint inflammation by week 52.

### ***certolizumab pegol (Cimzia)***

RAPID-axSpA is an ongoing multicenter, phase 3, randomized, double-blind, placebo-controlled, parallel-group trial in patients with axial spondyloarthritis (axSpA), including patients with ankylosing spondyloarthritis (AS).<sup>207</sup> While all patients met the criteria for axSpA, at least 50% of the patients had to meet the modified New York (mNY) criteria for radiographic diagnosis of AS. Patients were randomized to placebo or certolizumab pegol (CZP) 400 mg SC at weeks 0, 2, and 4 (loading dose) followed by either CZP 200 mg SC every 2 weeks or CZP 400 mg every 4 weeks. The doses were administered by unblinded, trained personnel at each site. All patients received injections every 2 weeks, either CZP or placebo, to maintain blinding. Patients were stratified by prior TNF inhibitor exposure. Patients assigned to placebo who did not achieve an Assessment of Spondyloarthritis International Society 20 (ASAS20) response at weeks 14 and 16 underwent mandatory escape at week 16 and were randomized to active treatment in a double blind fashion. Clinical primary endpoint was ASAS20 response at week 12, defined as an improvement of  $\geq 20\%$  and  $\geq 1$  unit on a 0 to 10 scale in greater than or equal to 3 of the following: Patients Global Assessment of Disease Activity (PTGADA), Pain assessment (total spinal pain on a 0 to 10 scale), Function (represented by a Bath Ankylosing Spondylitis Functional Index (BASFI), Inflammation (mean of BASDAI questions relating to morning stiffness) and no deterioration (worsening of  $> 20\%$  or 1 unit on a 0 to 10 scale) in the remaining area. A total of 325 patients were randomized to 1 of the 3 treatment arms. Of these, 178 patients (54.8%) met the mNY criteria for AS. Concomitant therapy with NSAIDs and DMARDs was allowed on the trial. Improvements in ASAS20 at week 12 in the AS subpopulation were 56.9% for CZP 200 mg every 2 weeks and 64.3% for CZP 400 mg every 4 weeks compared to 36.8% for placebo ( $p < 0.05$ ). The most common infectious adverse events were nasopharyngitis (8.8% CZP versus 6.5% placebo) and upper respiratory tract infections (4% CZP versus 2.8% placebo). The most common non-infectious adverse events were headache (6.2% CZP versus 6.5% placebo) and increased blood creatine phosphokinase (5.1% CZP versus 1.9% placebo). Increases in creatine phosphokinase were transient, and resolved spontaneously despite continued CZP therapy. No elevations were associated with an ischemic cardiac event or resulted in study discontinuation.

### ***etanercept (Enbrel)***

A double-blind study recruited 40 patients with active ankylosing spondylitis symptoms despite standard therapy.<sup>208</sup> Patients were randomly assigned to receive twice-weekly SC injections of etanercept 25 mg or placebo. At 4 months, significant improvement in symptoms, as determined by the primary composite endpoint of at least a 20% improvement in 3 of 5 measures of disease activity, was observed in 80% of etanercept patients compared to 30% of placebo patients ( $p = 0.004$ ). Etanercept treatment resulted in significant improvements over baseline in 4 of the 5 measures – duration of morning stiffness, nocturnal spine pain, patient assessment of disease activity and BASFI, the BASFI ( $p < 0.05$  for all comparisons to placebo) – but not for the mean swollen joint score. The etanercept group also had significant improvement in many of the secondary outcome measures, including Physician's global assessment of disease activity, chest expansion, enthesitis, ERS (erythrocyte sedimentation rate), and CRP (C-reactive protein). Placebo patients experienced a similar response to etanercept in an open-label, 6-month extension phase. There was no difference in the rates of adverse events between the 2 groups, nor were there any serious adverse events in either group.

Thirty patients with active ankylosing spondylitis refractory to NSAID therapy were randomized in double-blind fashion into 2 groups, receiving either etanercept 25 mg twice weekly or placebo for 6 weeks, after which both groups were treated with etanercept.<sup>209</sup> All patients received etanercept for a

total of 12 weeks and were followed up for at least 24 weeks. At week 6, 57% of patients treated with etanercept achieved the primary endpoint of at least a 50% improvement in the BASDAI compared to 6% of the placebo-treated patients ( $p=0.004$ ). There was ongoing improvement in all parameters in both groups throughout the period of etanercept treatment. Disease relapses occurred at an average of 6.2 weeks after cessation of etanercept. No severe adverse events, including major infections, were observed during the trial. Four patients withdrew from the study, 3 prior to receiving study drug and 1 after receiving 1 dose.

Two hundred seventy-seven patients with moderate to severe ankylosing spondylitis were recruited into a placebo-controlled, double-blind study of etanercept.<sup>210</sup> Patients were randomized to receive etanercept 25 mg or placebo twice weekly for 24 weeks. By 12 weeks, ASAS 20, the primary endpoint, was reached by 59% of patients in the etanercept group compared to 28% of patients in the placebo group ( $p<0.0001$ ). This rate of response was maintained, with 57% and 22% of patients in the etanercept and placebo groups, respectively, achieving ASAS 20 at the conclusion of the 24-week treatment period ( $p<0.0001$ ). All components of the ASAS, acute-phase reactant levels, and spinal mobility measures were significantly improved ( $p<0.05$  for all comparisons to placebo). Injection-site reactions, accidental injuries, and upper respiratory tract infections are the adverse events that occurred more frequently in the etanercept group. A 168-week open-label extension of the trial enrolled 257 of the 277 patients (92%) to evaluate long-term safety and efficacy of etanercept treatment in patients with ankylosing spondylitis.<sup>211</sup> Safety endpoints included rates of adverse events, infections, and death. Of patients who received etanercept in both the clinical trial and the open-label extension, 71% were ASAS 20 responders at week 96, and 81% were responders at week 192. Placebo patients who switched to etanercept in the open-label extension showed similar patterns of efficacy maintenance. After up to 192 weeks of treatment with etanercept, the most common adverse effects were injection site reactions, headaches, and diarrhea. The rate of infections was 1.1 per patient-year, and the rate for serious infections was 0.02 per patient-year. No deaths were reported.

### ***golimumab (Simponi)***

GO-RAISE study: The safety and efficacy of golimumab were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 356 adult patients with active AS according to modified New York criteria for at least 3 months (Study AS).<sup>212</sup> Patients had symptoms of active disease [defined as a BASDAI  $\geq 4$  and VAS for total back pain of  $\geq 4$ , on scales of 0 to 10 cm] despite current or previous NSAID therapy. Patients were excluded if they had complete ankylosis of the spine or if they were previously treated with a biologic TNF blocker. Patients were randomly assigned to golimumab 50 mg ( $n=138$ ), golimumab 100 mg ( $n=140$ ), or placebo ( $n=78$ ) administered SC every 4 weeks. Patients were allowed to continue stable doses of concomitant methotrexate, sulfasalazine, hydroxychloroquine, low dose corticosteroids, and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited. The primary endpoint was the percentage of patients achieving an ASAS 20 response at week 14 and was reported as 59.4% for golimumab 50 mg group, 60% for golimumab 100 mg group, and 21.8% for placebo-treated patients ( $p<0.001$ ). Placebo-controlled efficacy data were collected and evaluated through week 24. ASAS 40 response rates at week 24 were 43.5% for golimumab 50 mg group, 54.3% for golimumab 100 mg group, and 15.4% for placebo-treated group. There was no clear evidence of improved ASAS response with the higher golimumab dose group 100 mg compared to the lower golimumab dose group 50 mg. Eight golimumab-treated patients and 1 placebo-treated patient had markedly abnormal liver enzyme values

that were transient. Clinical improvements found at week 24 were continued through week 256 (5 years).<sup>213</sup>

### ***infliximab (Remicade)***

In a multicenter study, 70 patients with active symptoms of ankylosing spondylitis despite therapy with NSAIDs were enrolled in a placebo-controlled, double-blinded trial of infliximab 0.5 mg/kg IV given at 0, 2, and 6 weeks.<sup>214</sup> The primary endpoint, a 50% improvement in BASDAI between baseline and week 12, was achieved by 53% of patients in the active therapy group and 9% in the control group ( $p < 0.05$ ). Significant benefit of treatment with infliximab was observed in each individual parameter of the BASDAI. Significant benefit was also observed in parameters measuring disability, spinal mobility, quality of life (QoL), and acute phase reactants. Three patients on infliximab had serious events (TB, allergic bronchial granulomatosis, transient leukopenia) and were withdrawn from the study, compared to none on placebo ( $p = \text{NS}$ ). In a 12-week open-label extension, placebo patients who then received infliximab showed similar responses.

Of the 54 patients who completed the first year of this study, 52 continued to receive infliximab 5 mg/kg every 6 weeks up to week 102.<sup>215</sup> Forty-nine patients (71% of 69 enrolled patients and 94% of patients who started year 2) completed the study up to week 102. Improvement in signs and symptoms of ankylosing spondylitis seen during the first year of the study was sustained during the second year. Thirty (58%) patients achieved at least a 50% improvement from baseline in the BASDAI score, the primary endpoint, at week 102. Scores for other efficacy assessments were similar at weeks 54 and 102. Median CRP levels remained low at weeks 54 and 102 (3.9 and 4.3 mg/L, respectively). Side effects during the second year of the study were similar to those of the first year of treatment with infliximab.

In the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT), 357 patients with ankylosing spondylitis were randomly assigned to receive infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 12, and 18.<sup>216</sup> At 24 weeks, 61.2% of patients in the infliximab group were ASAS 20 responders compared with 19.2% of patients in the placebo group ( $p < 0.001$ ). Clinical benefit was observed in patients receiving infliximab as early as week 2 and was maintained over the 24-week study period. In addition, 22.4% of infliximab patients achieved partial remission. Patients receiving infliximab also showed significant improvements in the BASDAI, as well as the chest expansion and physical component summary score of the SF-36 short form health survey. Adverse events were reported by 82.2% of patients receiving infliximab and by 72% of patients receiving placebo. Most adverse events in both treatment groups were mild or moderate in severity. After 24 weeks of therapy in the above study, the placebo-treated ( $n = 78$ ) and the infliximab-treated ( $n = 201$ ) patients all received infliximab 5 mg/kg from week 24 to 96.<sup>217</sup> At week 102, the ASAS 20 responses for the patients initially assigned to placebo (72.1%) and for patients initially in infliximab (73.9%) were similar.

### ***secukinumab (Cosentyx)***

Two randomized, double-blind, placebo-controlled trials (MEASURE 1 and 2) assessed the efficacy of secukinumab for adults with AS. Patients with active disease, as defined by a BASDAI  $\geq 4$  despite NSAID, corticosteroid, or DMARD therapy.<sup>218,219</sup> Concomitant use of methotrexate (14%) or sulfasalazine (26%) were used in some patients, and approximately 33% of patients had discontinued prior treatment with an anti-TNF $\alpha$  due to either intolerance or lack of efficacy. MEASURE 1 ( $n = 371$ ) patients were randomized to IV secukinumab 10 mg/kg (unapproved dose) or placebo on weeks 0, 2, and 4, followed by either SC secukinumab 75 mg or 150 mg or placebo every 4 weeks thereafter. At

week 16, the ASAS 20, the primary endpoint, were 61%, 60%, and 29% for secukinumab 150 mg, secukinumab 75 mg, and placebo, respectively ( $p < 0.001$  for both secukinumab doses versus placebo). In MEASURE 2 ( $n=219$ ), patients were randomized to either SC secukinumab 75 mg or 150 mg or placebo on weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks thereafter. The primary endpoint was patients achieving ASAS 20 at week 16, at which point placebo patients were re-randomized to either active treatment dose. At week 16, 61% of patients using the 150 mg dose compared to 28% of patients on placebo achieved ASAS 20 (difference, 33%; 95% CI, 18 to 48). ASAS 20 for the 75 mg dose was 41% ( $p=0.1$  versus placebo). At week 16, 36% of patients using the 150 mg dose compared to 11% of patients on placebo achieved ASAS 40 (difference, 25%; 95% CI, 12 to 38).

## Crohn's Disease

### *adalimumab (Humira)*

A study measured the efficacy and safety of adalimumab in the maintenance of response and remission of Crohn's Disease (CD).<sup>220</sup> Patients ( $n=778$ ) received open-label induction therapy with adalimumab 80 mg (week 0) followed by 40 mg (week 2). At week 4, patients were stratified by response (decrease in Crohn's Disease Activity Index [CDAI]  $\geq 70$  points from baseline) and randomized to double-blind treatment with placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly through week 56. CDAI is used in clinical trials to measure disease activity. CDAI scores  $< 150$  indicate a clinical remission, and scores  $> 450$  indicate severely active disease. The primary endpoints were the percentages of randomized responders who achieved clinical remission (CDAI score  $< 150$ ) at weeks 26 and 56. The percentage of randomized responders in remission was significantly greater in the adalimumab every other week and adalimumab weekly groups versus placebo at week 26 (40%, 47%, and 17%, respectively;  $p < 0.001$ ) and week 56 (36%, 41%, and 12%, respectively;  $p < 0.001$ ). There were no significant differences in efficacy between the 2 adalimumab groups. Adverse events requiring discontinuation occurred more frequently in the placebo group (13.4%) than those receiving adalimumab every week (4.7%) or every other week (6.9%). Adalimumab every other week and weekly maintenance therapies were associated with 52% and 60% relative reductions in 12-month, all-cause hospitalization risk, and 48% and 64% reductions in 12-month risk of Crohn's Disease-related hospitalization.<sup>221</sup> Fewer Crohn's Disease-related surgeries occurred in the adalimumab every other week, weekly, and combined groups compared with placebo (0.4%, 0.8%, and 0.6% versus 3.8%, respectively; all  $p < 0.05$ ).<sup>222</sup>

A double-blind, placebo-controlled trial was designed to determine whether adalimumab induces remissions more frequently than placebo in 325 adult patients with Crohn's disease who have symptoms despite infliximab therapy or who cannot take infliximab because of adverse events.<sup>223</sup> Patients were included if they had a history of Crohn's disease for 4 months or more that was moderate to severe at baseline (CDAI score, 220 to 450 points). Patients were randomized to receive induction doses of adalimumab, 160 mg and 80 mg, at weeks 0 and 2, respectively, or placebo at the same time points. The primary endpoint was induction of remission at week 4. A total of 301 patients completed the trial. Remission was achieved at week 4 by 21% versus 7% for adalimumab group versus placebo ( $p < 0.001$ ). The absolute difference in clinical remission rates was 14.2 percentage points (95% CI, 6.7 to 21.6 percentage points). A 70-point response occurred at week 4 in 52% of patients in the adalimumab group versus 34% of patients in the placebo group ( $p=0.001$ ). Discontinuations due to adverse effects occurred in 2 patients in the adalimumab group and 4 patients in the placebo group.

Serious infections were reported in 4 patients receiving placebo and none of the patients receiving adalimumab.

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy of adalimumab in the healing of draining fistulas in 117 patients with active CD.<sup>224</sup> Patients were adults with moderate to severely active CD (CD activity index 220-450) for at least 4 months who had draining fistulas at baseline. All patients received open-label adalimumab induction therapy with 80 mg initially then 40 mg at week 2. At week 4, all patients were randomly assigned to receive double-blind placebo or adalimumab 40 mg every other week or weekly to week 56. Complete fistula healing/closure was defined as no drainage, either spontaneous or with gentle compression, by week 56. The mean number of draining fistulas per day was significantly decreased in adalimumab-treated patients compared with placebo-treated patients during the double-blind treatment period (0.88 with either dose of adalimumab versus 1.34 with placebo;  $p=0.002$ ).

### ***certolizumab pegol (Cimzia)***

In a randomized, double-blind, placebo-controlled study, the efficacy of certolizumab pegol was evaluated in 662 adults with moderate-to-severe Crohn's disease (PRECISE-1).<sup>225</sup> Patients who had received any anti-TNF agent within the previous 3 months or who had had a severe hypersensitivity reaction or a lack of response to the first dose of another TNF blocker were ineligible. Patients were stratified by baseline levels of CRP ( $\geq 10$  or  $< 10$  mg/L), use of glucocorticoids, and use of concurrent immunosuppressive drugs. Patients were randomized to certolizumab pegol 400 mg or placebo subcutaneously at weeks 0, 2, and 4 weeks, and then every 4 weeks following that. Response was defined as a decrease of at least 100 points in the CDAI score at week 6 and 26. Remission was defined as an absolute CDAI  $\leq 150$ . In patients with a baseline CRP level  $\geq 10$  mg/L, 37% of patients in the certolizumab pegol group had a response at week 6, as compared with 26% in the placebo group ( $p=0.04$ ). Twenty-two percent of patients in the certolizumab pegol group compared to 12% of patients in the placebo group had a response at both weeks 6 and 26 ( $p=0.05$ ). In the overall population, the response rates at week 6 for certolizumab pegol and placebo were 35% and 27%, respectively ( $p=0.02$ ). For both weeks 6 and 26, response rates were 23% and 16% for certolizumab pegol and placebo groups, respectively ( $p=0.02$ ). At weeks 6 and 26, the rates of remission in the 2 groups did not differ significantly ( $p=0.17$ ). A total of 154 patients assigned to placebo and 145 assigned to certolizumab pegol completed the study. Serious infections were reported in 2% of patients receiving certolizumab pegol and less than 1% of those patients who received placebo. In the certolizumab group, antibodies to the drug developed in 8% of patients and antinuclear antibodies developed in 2%. The study was supported by the manufacturer of certolizumab pegol.

In the double-blind PRECISE-2 study, efficacy of certolizumab pegol was evaluated in 668 adults with moderate to severe Crohn's disease as maintenance therapy.<sup>226</sup> Open-label induction therapy with certolizumab pegol 400 mg subcutaneously at weeks 0, 2, and 4 was administered. Baseline CDAI scores were 220-450. Thirty-eight percent of patients in each group were not receiving either glucocorticoids or immunosuppressives. A total of 428 patients had a clinical response at week 6. Patients with a clinical response at week 6 were stratified by baseline CRP level and were randomized to certolizumab pegol 400 mg ( $n=216$ ) or placebo ( $n=212$ ) every 4 weeks through week 24 with 2 weeks of additional follow-up. The study was completed by 109 patients assigned to the placebo group and 151 patients assigned to certolizumab pegol. The response was maintained through week 26 in 62% of the patients with a baseline CRP level of at least 10 mg/L, who were receiving certolizumab, compared to 34% in the placebo group ( $p<0.001$ ). Patients with a response to induction at week 6 and

remission (defined as CDAI score  $\leq 150$ ) at week 26 was achieved in 48% and 29% of the certolizumab pegol and placebo groups, respectively ( $p < 0.001$ ). Infectious serious adverse events (including 1 case of pulmonary tuberculosis) were reported in 3% of patients receiving certolizumab pegol and less than 1% of the patients receiving placebo. The study was supported by the manufacturer of certolizumab pegol.

### ***infliximab (Remicade)***

ACCENT I was a randomized study of the benefit of maintenance therapy with infliximab in patients with active Crohn's disease who respond to a single IV infusion of infliximab.<sup>227</sup> In this study, 573 patients received infliximab 5 mg/kg. They were assessed 2 weeks later, at which time responders, defined as seeing a decrease in CDAI score of at least 70 points and 25% from baseline, were randomized into 1 of 3 groups: high-dose infliximab (5 mg/kg at weeks 2 and 6 followed by 10 mg/kg every 8 weeks until week 46), low-dose infliximab (5 mg/kg at the same time points), or placebo. The primary endpoints were: 1) the proportion of patients who responded at week 2 and were in remission at week 30, and 2) the time to loss of response up to week 54. Fifty-eight percent of the patients responded to the single infusion of infliximab at 2 weeks. At 30 weeks, 21% of the placebo patients were in remission, compared to 45% of high-dose ( $p = 0.0002$ ) and 39% of low-dose ( $p = 0.003$ ) infliximab patients. Throughout the 54-week trial, the median time to loss of response was  $> 54$  weeks and 38 weeks for high- and low-dose infliximab patients, respectively, compared with 19 weeks for the placebo group ( $p = 0.0002$  and  $0.002$ , respectively). The safety profile of infliximab was similar to other studies; the incidence of serious infections was similar across treatment groups. ACCENT I substudies showed that infliximab improved health-related quality of life.<sup>228</sup>

An ACCENT II substudy examined the effect of infliximab maintenance treatment on hospitalizations, surgeries, and procedures in patients with fistulizing Crohn's disease.<sup>229</sup> After receiving infliximab 5 mg/kg at weeks 0, 2, and 6, patients were separately randomized at week 14 as responders (195 patients) or nonresponders (87 patients) to receive placebo or to continue with infliximab maintenance therapy every 8 weeks. Among patients randomized as responders, those who received infliximab maintenance had significantly fewer mean hospitalization days (0.5 versus 2.5 days;  $p < 0.05$ ), mean number of hospitalizations (11/100 patient versus 31/100 patients;  $p < 0.05$ ), total surgeries and procedures (65 versus 126;  $p < 0.05$ ), inpatient surgeries and procedures (7 versus 41;  $p < 0.01$ ), and major surgeries (2 versus 11;  $p < 0.05$ ), compared with those who received placebo maintenance.

### ***vedolizumab (Entyvio)***<sup>230</sup>

Three randomized, double-blind, placebo-controlled clinical trials (CD Trials I, II, and III) were conducted to evaluate the safety and efficacy of vedolizumab in adult patients with moderately to severely active CD (CDAI score of 220 to 450). Enrolled patients in the U.S. had over the previous 5-year period an inadequate response or intolerance to immunomodulator therapy (e.g., thiopurines [azathioprine or mercaptopurine] or methotrexate) and/or an inadequate response, loss of response, or intolerance to one or more TNF blockers. Outside the U.S., prior treatment with corticosteroids was sufficient for entry if, over the previous 5-year period, the patients were corticosteroid dependent or had an inadequate response or intolerance to corticosteroids. Patients that had ever received natalizumab and patients that had received a TNF blocker in the past 60 days were excluded from enrollment.

In CD Trial I, 368 patients were randomized in a double-blind fashion (3:2) to receive vedolizumab 300 mg or placebo by IV infusion at 0 and 2 weeks with efficacy assessments at 6 weeks. Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were permitted through

Week 6. At baseline, patients were receiving corticosteroids (49%), immunomodulators (35%), and/or aminosaliclates (46%). A total of 48% of the patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. The median baseline CDAI score was 324 in the vedolizumab group and 319 in the placebo group. In the trial, a statistically significantly higher percentage of patients treated with vedolizumab achieved clinical remission (defined as CDAI  $\leq$  150) as compared to placebo (15% versus 7%,  $p=0.041$ ) at Week 6. The difference in the percentage of patients who demonstrated clinical response (defined as a  $\geq$  100 point decrease in CDAI score from baseline) was not, however, statistically significant at Week 6.

In CD Trial II, 416 patients were randomized in a double-blind fashion (1:1) to receive either vedolizumab 300 mg or placebo at 0, 2, and 6 weeks and efficacy assessments occurred at 6 and 10 weeks. The trial enrolled a higher number of patients who had over the previous 5-year period had an inadequate response, loss of response, or intolerance to 1 or more TNF blockers (76%) than CD Trial I. Concomitant aminosaliclates, corticosteroids, and immunomodulators were permitted through Week 10. At baseline, patients were receiving corticosteroids (54%), immunomodulators (34%), and aminosaliclates (31%). The median baseline CDAI score was 317 in the vedolizumab group and 301 in the placebo group. For the primary endpoint of clinical remission at Week 6, treatment with vedolizumab did not result in statistically significant improvement over placebo.

In CD Trial III, 461 patients who had a clinical response to vedolizumab at week 6 were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at week 6: vedolizumab 300 mg every 8 weeks, vedolizumab 300 mg every 4 weeks, or placebo every 4 weeks. Concomitant aminosaliclates and corticosteroids were permitted through week 52 and efficacy assessments were conducted at week 52. Concomitant immunomodulators were permitted outside the U.S. but were not permitted beyond week 6 in the U.S. At week 6, patients were receiving corticosteroids (59%), immunomodulators (31%), and aminosaliclates (41%). A total of 51% of patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. At week 6, the median CDAI score was 322 in the vedolizumab every 8 week group, 316 in the vedolizumab every 4 week group, and 315 in the placebo group. Patients who had achieved clinical response at week 6 and were receiving corticosteroids were required to begin a corticosteroid tapering regimen at week 6. In the trial, a greater percentage of patients in groups treated with vedolizumab as compared to placebo (39% versus 22%,  $p=0.001$ ) were in clinical remission at week 52. A greater percentage of patients in groups treated with vedolizumab, as compared to placebo (44% versus 30%,  $p=0.013$ ), had a clinical response at week 52. The vedolizumab every 4-week dosing regimen did not demonstrate additional clinical benefit over the every 8-week dosing regimen and is not the recommended dosing regimen.

## **Cryopyrin-Associated Periodic Syndromes (CAPS)**

### ***anakinra (Kineret)*<sup>231</sup>**

The efficacy of anakinra was evaluated in a prospective, long-term, open-label and uncontrolled study which incorporated a withdrawal period in a subset of 11 patients. This study included 43 Neonatal-Onset Multisystem Inflammatory Disease (NOMID) patients 0.7 to 46 years of age treated for up to 60 months. Patients were given an initial anakinra dose of 1 to 2.4 mg/kg body weight. During the study, the dose was adjusted by 0.5 to 1 mg/kg increments to a protocol-specified maximum of 10 mg/kg daily, titrated to control signs and symptoms of disease. The average maintenance dose was 3 to 4 mg/kg daily. In general, the dose was given once daily, but for some patients, the dose was split into twice daily administrations for better control of disease activity. NOMID symptoms were assessed with

a disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache. Mean change in DSSS score was -3.5 (95% CI, -3.7 to -3.3) at months 3 to 6 and -3.5 (95% CI, -3.8 to -3.1) at month 60. For the 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of anakinra therapy.

### ***canakinumab (Ilaris)*<sup>232</sup>**

The efficacy and safety of canakinumab for the treatment of CAPS was demonstrated in a 3-part trial in patients in 31 patients 9 to 74 years of age with the Muckle-Wells Syndrome (MWS) phenotype of CAPS. Throughout the trial, patients weighing more than 40 kg received canakinumab 150 mg and patients weighing 15 kg to 40 kg received 2 mg/kg. Part 1 was an 8-week open-label, single-dose period where all patients received canakinumab. Patients who achieved a complete clinical response and did not relapse by week 8 were randomized into part 2, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed part 2 or experienced a disease flare entered part 3, a 16-week open-label active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and had serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10 mg/L. A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD.

In Part 1, a complete clinical response was observed in 71% of patients 1 week following initiation of treatment and in 97% of patients by Week 8. In Part Two, 16 patients were randomized to the placebo group and 15 were randomized to the canakinumab group. A total of 13 patients (81%) of the patients randomized to placebo flared as compared to none of the patients randomized to canakinumab (95% CI, 53% to 96%). At the end of Part 2, all 15 patients treated with canakinumab had absent or minimal disease activity and skin disease. CRP and SAA values subsequently normalized in the placebo group after reintroduction of canakinumab in Part 3.

### ***rilonacept (Arcalyst)*<sup>233</sup>**

The safety and efficacy of rilonacept for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with 2 parts (A and B) conducted sequentially in the same patients with FCAS (Familial Cold Autoinflammatory Syndrome) and MWS phenotypes of CAPS. Part A was a 6-week, randomized, double-blind, parallel-group period comparing rilonacept at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all subjects received rilonacept 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on rilonacept 160 mg weekly or to receive placebo. Using a daily diary questionnaire, patients rated the following 5 signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment. The patients in the rilonacept group had a larger reduction than the placebo (-2.4 versus -0.5; 95% CI, -2.4 to -1.3) in the mean symptom score in Part A. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on rilonacept (0.9 versus 0.1; 95% CI, -1.3 to -0.4).

## Hidradenitis Suppurativa (HS)

### ***adalimumab (Humira)***

Two randomized, double-blind, placebo-controlled studies evaluated the safety and efficacy of adalimumab in adults with moderate to severe HS, defined as those with Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules (n=633).<sup>234</sup> Patients were randomized to placebo or adalimumab 160 mg on week 0, 80 mg on week 2, and 40 mg on week 4 and every week thereafter through week 11. Concomitant oral antibiotic use was allowed in study 2 (occurred in 19.3% of patients), and patients used topical antiseptic wash daily in both studies. The primary endpoint in both trials was Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula compared to baseline. HS-related pain was assessed on a numeric 11-point scale in patients with a score of  $\geq 3$  at baseline. At week 12, 42% of patients treated with adalimumab and 26% of patients on placebo in study 1 (n=307) and 59% of patients treated with adalimumab and 28% of patients on placebo in study 2 (n=326) achieved response (HiSCR). From week 12 to 35, patients assigned to adalimumab were re-randomized to 40 mg weekly, 40 mg every other week, or placebo. In those reassigned to placebo following adalimumab treatment, 22% (22 of 100) developed flares, defined as  $\geq 25\%$  increase in abscess and inflammatory nodule count (minimum of 2 additional lesions) from baseline.

## Plaque Psoriasis

For this indication, the Psoriasis Area and Severity Index (PASI) is the measure of efficacy. The PASI score is a composite score that takes into consideration both the fraction of the body surface area (BSA) affected and the nature and severity of psoriatic changes within the affected regions (erythema, infiltration/plaque thickness, and desquamation). The PASI 75, which reflects a 75% or greater improvement in symptoms, is often considered the “gold standard” and is reported when available. When the PASI is not specified, it may be useful to consider that a median reduction in PASI score of 68% correlates to approximately 40% of patients achieving the PASI 75.

### ***adalimumab (Humira)***

A multicenter, randomized, double-blind, placebo-controlled trial of 147 patients with moderate to severe plaque psoriasis were treated with adalimumab 40 mg every other week, 40 mg every week, or placebo for 12 weeks and then could continue in a 48-week extension trial.<sup>235</sup> Patients taking placebo were switched to adalimumab for the extension trial. After 12 weeks of adalimumab treatment, 53% of patients taking adalimumab every other week, 80% of patients taking weekly adalimumab, and 4% of patients receiving placebo achieved 75% improvement in PASI score ( $p < 0.001$ ). These responses were sustained for the full 60 weeks. The study was insufficiently powered to detect rare adverse effects associated with adalimumab treatment.

A 52-week, multicenter, randomized, placebo-controlled study investigated the efficacy and safety of adalimumab 40 mg for the treatment of moderate to severe psoriasis.<sup>236</sup> A total of 1,212 patients were randomized to adalimumab 40 mg or placebo every other week for the first 15 weeks. Patients were evaluated at week 16; 71% of the adalimumab-treated and 7% of placebo-treated patients showed at least a 75% improvement in PASI score. During weeks 33 to 52, the percentage of patients re-randomized to placebo who lost adequate response (defined as  $< 50\%$  improvement in the PASI

response relative to baseline and at least a 6-point increase in PASI score from week 33) was 28% compared with 5% of patients treated continuously with adalimumab.

The CHAMPION study was a 16-week study to compare adalimumab and methotrexate in 271 patients with psoriasis.<sup>237</sup> Patients with moderate to severe plaque psoriasis were randomized to adalimumab (80 mg SC at week 0, then 40 mg every other week, n=108), methotrexate (7.5 mg orally, increased as needed and as tolerated to 25 mg weekly; n=110) or placebo (n=53) for 16 weeks. The primary efficacy endpoint was the proportion of patients achieving at least a 75% improvement in the PASI 75 after 16 weeks. After 16 weeks, the percent of patients achieving PASI 75 was 79.6% of adalimumab-treated patients, 35.5% for methotrexate (p<0.001 versus adalimumab), and 18.9% for placebo (p<0.001 versus adalimumab). Statistically significantly more adalimumab-treated patients (16.7%) than methotrexate-treated patients (7.3%) or placebo-treated patients (1.9%) achieved complete clearance of disease. Adverse events were similar in all the groups.

### ***apremilast (Otezla)***

Two multicenter, randomized, double-blind, placebo-controlled trials (Studies PSOR-1 and PSOR-2, also referred to as ESTEEM 1 and ESTEEM 2) enrolled a total of 1,257 subjects 18 years of age and older with moderate to severe plaque psoriasis.<sup>238,239</sup> Subjects were allowed to use low-potency topical corticosteroids on the face, axilla, and groin. Subjects with scalp psoriasis were allowed to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. Study PSOR-1 enrolled 844 subjects and Study PSOR-2 enrolled 413 subjects. In both studies, subjects were randomized 2:1 to apremilast 30 mg twice daily or placebo for 16 weeks. Both studies assessed the proportion of subjects who achieved PASI-75 at Week 16 and the proportion of subjects who achieved a static Physician Global Assessment (sPGA) score of clear (0) or almost clear (1) at week 16. Across both studies, subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. The mean baseline BSA involvement was 25.19% (median 21%), the mean baseline PASI score was 19.07 (median 16.8), and the proportion of subjects with sPGA score of 3 (moderate) and 4 (severe) at baseline were 70% and 29.8%, respectively. In both studies (PSOR-1 and PSOR-2), the PASI-75 and sPGA were statistically significantly higher in the apremilast group when compared to placebo (PSOR-1 PASI-75 33.1% versus 5.3% and sPGA 21.7% versus 3.9%, PSOR-2 PASI-75 28.8% versus 5.8% and sPGA 20.4% versus 4.4%; p values < 0.05). In an *a priori* subgroup analysis of ESTEEM 1 and ESTEEM 2, improvement in nail and moderate to very severe scalp psoriasis at week 16 was also significantly superior to placebo; however, the groups were not stratified by these conditions.<sup>240</sup>

### ***etanercept (Enbrel)***

A double-blind study enrolled 583 adult patients with active, clinically stable plaque psoriasis involving at least 10% of BSA, with a minimum PASI of 10 at screening and who had received or were a candidate to receive systemic psoriasis therapy or phototherapy.<sup>241</sup> During the first 12 weeks of the study, patients were randomly assigned to receive etanercept 25 or 50 mg or placebo twice weekly as subcutaneous injections. During the second 12 weeks, all patients received etanercept 25 mg twice weekly. The primary endpoint, a PASI 75 response at week 12, was achieved by 49% of patients in the etanercept 50 mg group, 34% in the 25 mg group, and 3% in the placebo group (p<0.0001 for each etanercept group compared with placebo). At week 24 (after 12 weeks of open-label etanercept 25 mg twice weekly), a PASI 75 was achieved by 54% of patients whose dose was reduced from 50 mg to 25 mg twice weekly, by 45% of patients in the continuous 25 mg twice weekly group, and by 28% in the

group that received placebo followed by etanercept 25 mg twice weekly. Etanercept was well tolerated throughout the study.

### ***ixekizumab (Taltz)***

Three multicenter, randomized, double-blind, placebo-controlled trials (Trials 1, 2, and 3) assessed the efficacy of ixekizumab in adult patients with plaque psoriasis who were candidates for phototherapy or systemic therapy (n=3,866).<sup>242,243</sup> Patients were required to have a minimum BSA involvement of 10%, sPGA score of  $\geq 3$  in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 5, and PASI score  $\geq 12$ . In all trials, subjects were randomized to either placebo or ixekizumab (80 mg every 2 weeks for 12 weeks following a 160 mg starting dose). In addition, 2 studies included an active comparator arm (Trials 2 and 3), in which subjects were also randomized to etanercept 50 mg twice weekly for 12 weeks. All the trials evaluated the changes from baseline to week 12 in the 2 co-primary endpoints: 1) PASI 75; and 2) sPGA of “0” (clear) or “1” (minimal), the proportion of subjects with an sPGA 0 or 1 and at least a 2-point improvement. Other evaluated outcomes included the proportion of subjects with an sPGA score of 0 (clear), a reduction of at least 90% in PASI (PASI 90), a reduction of 100% in PASI (PASI 100), and an improvement of itch severity as measured by a reduction of at least 4 points on an 11-point itch Numeric Rating Scale. Median baseline PASI score ranged from approximately 17 to 18. Baseline sPGA score was severe or very severe in 51% of subjects in Trial 1, 50% in Trial 2, and 48% in Trial 3. Of all subjects, 44% had received prior phototherapy, 49% had received prior conventional systemic therapy, and 26% had received prior biologic therapy for the treatment of psoriasis.

At week 12, the percentage of patients that experienced an sPGA score of “0” or “1” in the every 2 week ixekizumab group versus the placebo group was 82% versus 3% (Trial 1), 83% versus 2% (Trial 2), and 81% versus 7% (Trial 3).<sup>244,245</sup> At week 12, the percentage of patients that experienced at least a 75% reduction in their PASI composite score in the every 2 week ixekizumab group versus the placebo group was 89% versus 4% (Trial 1), 90% versus 2% (Trial 2), and 87% versus 7% (Trial 3). The differences between the ixekizumab group and the placebo group all fell within the 95% confidence interval with a  $p < 0.0001$  for the respective endpoints. At week 12, the percentage of patients that experienced an sPGA score of “0” or “1” in the every 2 week ixekizumab group versus the etanercept group was 83% versus 36% (Trial 2), and 81% versus 42% (Trial 3). At week 12, the percentage of patients that experienced at least a 75% reduction in their PASI composite score in the every 2 week ixekizumab group versus the etanercept group was 90% versus 42% (Trial 2), 87% versus 53% (Trial 3). These differences between the ixekizumab group and the etanercept group all fell within the 95% confidence interval with a  $p < 0.0001$  for the respective endpoints.

Patients originally randomized to ixekizumab in Trial 1 and Trial 2 who were responders at week 12 (sPGA of 0 or 1) were re-randomized to an additional 48 weeks of either a maintenance dose of ixekizumab 80 mg every 4 weeks or placebo to evaluate the maintenance and durability of response.<sup>246</sup> Furthermore, ixekizumab non-responders (sPGA  $> 1$ ) and subjects who relapsed (sPGA  $\geq 3$ ) during the maintenance period were placed on ixekizumab 80 mg every 4 weeks. For patients who were responders at Week 12, the percent who maintained a response (an sPGA of “0” or “1”) at the end of week 60 was higher for the ixekizumab group compared to the placebo group (75% versus 7%, respectively). The median time to relapse (sPGA  $\geq 3$ ) was 164 days for responders at Week 12 who got re-randomized to treatment withdrawal and received placebo. Of the patients re-randomized to receive placebo, 66% regained a response of at least “0” or “1” within 12 weeks of restarting treatment with ixekizumab every 4 weeks.

### ***secukinumab (Cosentyx)***

Four randomized, double-blind, placebo-controlled, multicenter trials (trials 1, 2, 3, and 4) enrolled 2,403 patients (691 randomized to secukinumab 300 mg, 692 to secukinumab 150 mg, 694 to placebo, and 323 to a biologic active control) 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and PASI  $\geq 12$ , and who were candidates for phototherapy or systemic therapy.<sup>247,248</sup> In all trials, the endpoints were the proportion of subjects who achieved a reduction in PASI  $\geq 75\%$  (PASI 75) from baseline to week 12 and treatment success (clear or almost clear) on the Investigator's Global Assessment modified 2011 (IGA). Other evaluated outcomes included the proportion of subjects who achieved a reduction in PASI score of at least 90% (PASI 90) from baseline at week 12, maintenance of efficacy to week 52, and improvements in itching, pain, and scaling at week 12 based on the Psoriasis Symptom Diary.

PASI 90 response at week 12 was achieved with secukinumab 300 mg and 150 mg compared to placebo in 59% (145/245) and 39% (95/245) versus 1% (3/248) of subjects, respectively (Trial 1: ERASURE trial) and 54% (175/327) and 42% (137/327) versus 2% (5/326) of patients, respectively (Trial 2: FIXTURE trial). Similar results were seen in Trials 3 and 4. With continued treatment over 52 weeks, subjects in Trial 1 who were PASI 75 responders at week 12 maintained their responses in 81% (161/200) of the subjects treated with secukinumab 300 mg and in 72% (126/174) of subjects treated with secukinumab 150 mg. Trial 1 patients who were clear or almost clear on the IGA at week 12 also maintained their responses in 74% (119/160) of subjects treated with secukinumab 300 mg and in 59% (74/125) of subjects treated with secukinumab 150 mg. Similarly in Trial 2, PASI 75 responders maintained their responses in 84% (210/249) of subjects treated with secukinumab 300 mg and in 82% (180/219) of subjects treated with secukinumab 150 mg. Trial 2 subjects who were clear or almost clear on the IGA also maintained their responses in 80% (161/202) of subjects treated with secukinumab 300 mg and in 68% (113/167) of patients treated with secukinumab 150 mg. The manufacturer of secukinumab sponsored the study.

### ***secukinumab (Cosentyx) versus ustekinumab (Stelara)***

A randomized, double-blind, 52-week trial compared the efficacy of secukinumab to ustekinumab in the treatment of adult patients with moderate to severe plaque psoriasis (n=676).<sup>249</sup> Patients with inadequate control from topical treatments, phototherapy, and/or previous systemic therapy, but without prior exposure to biologics targeting IL-17 or IL-12/IL-23, were randomized 1:1 to SC secukinumab 300 mg or ustekinumab dosed based on body weight (both per labeling). The primary endpoint was 90% improvement in PASI (PASI 90) at week 16. At week 16, a greater percentage of patients in the secukinumab group (79%) achieved PASI 90 compared to ustekinumab (57.6%;  $p < 0.0001$ ). A significant difference was also seen between groups in PASI 100 and PASI 75 at week 16 ( $p \leq 0.001$ ). Adverse effects were reported in over half the population in each group with infections being the most commonly reported adverse effect; however, most infections were considered to be nonserious and did not lead to discontinuation. The authors concluded that secukinumab was superior to ustekinumab in the treatment of moderate to severe psoriasis. This trial was funded by the manufacturer of secukinumab.

### ***ustekinumab (Stelara) versus etanercept (Enbrel)***

In the treatment of moderate to severe psoriasis, ustekinumab and etanercept were compared in a single-blind, randomized trial with 903 patients.<sup>250</sup> Patients were randomized to either ustekinumab SC 45 or 90 mg at weeks 0 and 4 or etanercept SC 50 mg twice weekly for 12 weeks. The primary endpoint

was the proportion of patients with at least 75% improvement in PASI at week 12. The secondary endpoint was the proportion of patients with cleared or minimal disease based on the physician's global assessment. Assessors were blinded to the treatment. The proportion of patients achieving 75% improvement on PASI at week 12 were 67.5% of ustekinumab 45 mg group, 73.8% of the ustekinumab 90 mg group, and 56.8% of the etanercept group ( $p=0.01$  and  $p<0.001$ , respectively). For the physician's global assessment, 65.1%, 70.6%, and 49% of patients had cleared or minimal disease, respectively ( $p<0.001$  for both comparisons). Patients who did not have a response to etanercept were crossed over to ustekinumab therapy for 12 weeks; 48.9% had at least 75% improvement in the PASI within 12 weeks of crossover. Serious adverse events were reported in 1.9, 1.2, and 1.2% of the ustekinumab 90 mg and 45 mg groups and etanercept group, respectively. Safety patterns were similar before and after crossover from etanercept to ustekinumab. The manufacturer of ustekinumab sponsored the study.

### ***ustekinumab (Stelara)***

Two multicenter, randomized, double-blind, placebo-controlled trials were conducted to study ustekinumab. Both studies enrolled subjects 18 years of age or older with moderate to severe plaque psoriasis who had a minimum body surface area involved of 10% a PASI of 12 or greater, and who were candidates for phototherapy or systemic therapy. Subjects were randomized to placebo, ustekinumab 45 mg, or ustekinumab 90 mg. Subjects randomized to ustekinumab received the agent at weeks 0, 4, and 16. Subjects randomized to receive placebo crossed over to ustekinumab at weeks 12 and 16. The endpoints of both trials were the proportion of subjects who achieved at least a 75% in PASI score from baseline to week 12 and treatment success on the Physician's Global Assessment (PGA).

PHOENIX 1 enrolled a total of 766 subjects evaluated through week 52.<sup>251</sup> At week 12, 67.1% of those receiving 45 mg of ustekinumab, 66.4% of those receiving 90 mg of ustekinumab, and 3.1% of those receiving placebo achieved the PASI 75 response (difference in response rate versus placebo 63.9% [95% CI, 57.8 to 70.1;  $p<0.0001$ ] for 45 mg and 63.3% [95% CI, 57.1 to 69.4;  $p<0.0001$ ] for 90 mg). At week 12, a total of 59% of those receiving 45 mg of ustekinumab, 61% of those receiving 90 mg of ustekinumab, and 4% of those receiving placebo achieved a PGA score indicating "cleared" or "minimal." Of the patients initially randomized to ustekinumab at week 0 who achieved a long-term response (defined as 75% improvement in PASI 75) at weeks 28 and 40 were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment until loss of response. At week 40, long-term response had been achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group. Of these, 162 patients were randomly assigned to maintenance ustekinumab and 160 to withdrawal. At 1 year, PASI 75 response was better maintained in those receiving maintenance ustekinumab than those withdrawn from treatment ( $p<0.0001$ ). Serious adverse events were reported in 1.2% of patients receiving ustekinumab and 0.8% receiving placebo. Long-term safety data demonstrated consistent adverse effects over 3 years.<sup>252</sup>

PHOENIX 2 enrolled a total of 1,230 subjects with moderate to severe psoriasis.<sup>253</sup> At week 12, 66.7% of those receiving 45 mg of ustekinumab, 75.7% of those receiving 90 mg of ustekinumab, and 3.7% of those receiving placebo achieved the PASI 75 response (difference in response rate 63.1% [95% CI, 58.2 to 68;  $p<0.0001$ ] for the 45 mg group versus placebo and 72% [95% CI, 67.5 to 76.5;  $p<0.0001$ ] for the 90 mg group versus placebo). At week 12, a total of 68% of those receiving 45 mg of ustekinumab, 73% of those receiving 90 mg of ustekinumab, and 4% of those receiving placebo achieved a PGA score indicating "cleared" or "minimal."

## Psoriatic Arthritis

### ***adalimumab (Humira)***

Patients with moderately to severely active PsA and a history of inadequate response to NSAIDs were randomized to receive adalimumab 40 mg or placebo SC every other week for 24 weeks.<sup>254</sup> At week 12, 58% of the adalimumab-treated patients achieved an ACR 20 response, a primary endpoint, compared with 14% of the placebo-treated patients ( $p<0.001$ ). An ACR 20 response requires a patient to have a 20% reduction in the number of swollen and tender joints, and a reduction of 20% in 3 of the following 5 parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and degree of disability in Health Assessment Questionnaire (HAQ) score. ACR 30, 50, 70, 90, and 100 responses follow accordingly. At week 24, similar ACR 20 response rates were maintained and the mean change in the modified total Sharp score (mTSS, a measurement of erosion and joint space narrowing) was significantly improved in patients receiving adalimumab compared to those receiving placebo ( $p<0.001$ ). Of the adalimumab-treated patients, 59% achieved a PASI 75 response at 24 weeks, compared with 1% of patients treated with placebo ( $p<0.001$ ). Adalimumab was generally safe and well tolerated.

Patients ( $n=313$ ) who completed the 24-week, double-blind, Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) study versus placebo in PsA could elect to receive open-label adalimumab 40 mg subcutaneously every other week after week 24.<sup>255</sup> After 48 weeks, patients from the adalimumab arm of ADEPT ( $n=151$ ) had achieved ACR 20, ACR 50, and ACR 70 response rates of 56%, 44%, and 30%, respectively. A total of 69 patients were evaluated with PASI 50, PASI 75, PASI 90, and PASI 100 response rates and results are reported as follows: 67%, 58%, 46%, and 33%, respectively. Improvements in disability, as measured by the Disability Index of the Health Assessment Questionnaire (HAQ DI), were sustained from week 24 to week 48. The HAQ DI is a self-administered questionnaire that patients can complete easily and rapidly and that gives important information about prognosis, patient status, and changes in disease course over time. Adalimumab demonstrated clinical and radiographic efficacy regardless of whether patients were receiving methotrexate at baseline and was generally safe and well tolerated through week 48. After 2 years of treatment with adalimumab 40 mg every other week, patients ( $n=245$ ) continued to exhibit inhibition of radiographic progression and improvements in joint disease were maintained.<sup>256</sup> Long-term adverse effects were similar to those reported in the 24-week study with adalimumab.

In a placebo-controlled, double-blind, randomized, multicenter study, 100 patients with active PsA with an inadequate response to DMARDs were treated for 12 weeks with adalimumab 40 mg every other week or placebo.<sup>257</sup> The primary efficacy endpoint was the percentage of patients who met the ACR 20 core criteria at week 12. At week 12, an ACR 20 response was achieved by 39% of adalimumab patients versus 16% of placebo patients ( $p=0.012$ ). At week 12, measures of skin lesions and disability were statistically significantly improved with adalimumab. After week 12, open-label adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR 20 response rates of 65% and 57%, respectively, observed at week 24. Adverse effects were similar in frequency.

### ***apremilast (Otezla)***

The safety and efficacy of apremilast were evaluated in 3 randomized, double-blind, placebo-controlled, multicenter trials (Studies PsA-1, PsA-2, and PsA-3) of similar design. A total of 1,493 adult patients with active psoriatic arthritis (PsA) (3 swollen joints and 3 tender joints) despite prior or current treatment with DMARD therapy were randomized.<sup>258</sup> Patients enrolled in these studies had a diagnosis of PsA for at least 6 months. Previous treatment with a biologic, including TNF-blockers was allowed (up to 10% could be TNF-blocker therapeutic failures). Across the 3 studies, patients were randomly assigned to placebo (n=496), apremilast 20 mg (n=500), or apremilast 30 mg (n=497) given orally twice daily. Titration was used over the first 5 days. Patients were allowed to receive stable doses of concomitant methotrexate (25 mg/week), sulfasalazine, leflunomide, low dose oral corticosteroids, and/or NSAIDs during the trial. The patients who were therapeutic failures of greater than 3 agents for PsA (small molecules or biologics), or more than 1 biologic TNF blocker were excluded. The primary endpoint was the percentage of patients achieving ACR 20 response at week 16. In all 3 studies (PsA-1, PsA-2, and PsA-3), the week ACR 20 response was statistically significantly higher in the apremilast group when compared to placebo (PsA-1 38% versus 19 %, PsA-2 32% versus 19% and PsA-3 41% versus 18%;  $p < 0.05$  for both).

### ***certolizumab pegol (Cimzia)***

RAPID-PsA is a phase 3, double-blind, placebo-controlled study of certolizumab in patients with psoriatic arthritis.<sup>259</sup> A total of 409 adult ( $\geq 18$  years) patients were randomized to 1 of 3 arms: placebo, certolizumab pegol (CZP) 200 mg SC every 2 weeks, or CZP 400 mg every 4 weeks. Patients on the active treatment arms also received a loading dose of CZP 400 mg SC at weeks 0, 2, and 4 and then preceded on to the assigned maintenance dose arms. The drug was administered by investigators at each site using a blinded prefilled syringe. Patients at each site were stratified by prior exposure to TNF inhibitor. Placebo patients who failed to achieve a 10% improvement from baseline in both swollen and tender joints at weeks 14 and 16 underwent mandatory escape to active treatment in a blinded manner. A total of 59 (43.4%) of placebo patients were re-randomized to CZP treatment at week 16. The primary clinical endpoint of the study was ACR 20 response at week 12. The radiographic primary endpoint of the trial was change from baseline to week 24. Concomitant DMARDS were used by 70.2% of patients at baseline through week 24. At week 12, significantly more patients in the CZP 200 mg SC every 2 weeks and CZP 400 mg SC every 4 weeks achieved an ACR 20 response compared to placebo patients (58% and 51.9% versus 24.3%;  $p < 0.001$  for both). Patients treated with CZP 200 mg SC every 2 weeks demonstrated greater reduction in radiographic progression compared to placebo-treated patients at week 24 as measured by change in baseline in total modified total Sharp score (mTSS) (0.18 in placebo group compared with -0.02 in CZP 200 mg SC every 2 weeks group (95% CI, -0.38 to 0.04). Patients treated with CZP 400 mg SC every 4 weeks did not demonstrate greater inhibition of radiographic progression compared with placebo-treated patients at week 24. The most common non-infectious adverse events were diarrhea (3.6% CZP versus 2.9% placebo) and headache (3.6% CZP versus 1.5% placebo). The most common infectious adverse effects were nasopharyngitis (8.7% CZP versus 7.4% placebo) and upper respiratory tract infection (7.8% CZP versus 5.1% placebo).

### ***etanercept (Enbrel)***

Investigators randomized 205 patients with PsA to receive etanercept 25 mg or placebo twice weekly for 24 weeks.<sup>260</sup> Patients continued to receive blinded therapy in a maintenance phase until all had completed the 24-week phase, at which point they could receive open-label etanercept in a 48-week

extension. At 12 weeks, 59% of etanercept patients achieved an ACR 20 response (the primary outcome) compared with 15% of placebo patients ( $p < 0.0001$ ); results were sustained at 24 and 48 weeks. At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least a PASI 75 score, compared with 3% of placebo patients ( $p = 0.001$ ). Etanercept was well tolerated. This study confirmed the findings of an earlier, smaller clinical trial that was the first placebo-controlled trial of an anti-TNF medication for this indication.<sup>261</sup>

In a continuation of the above study, patients were permitted to continue in an open-label extension where all patients received etanercept 25 mg twice weekly.<sup>262</sup> Radiographic progression was monitored at baseline, 1, and 2 years using the Sharp method, modified to include joints frequently affected by PsA. A total of 169 patients continued therapy, 141 of them previously randomized to placebo and 70 previously randomized to etanercept, and were followed out to 2 years. ACR 20, PsARC, and PASI 50 criteria were met by 64%, 84%, and 62%, respectively, of etanercept/etanercept patients at the end of the 48-week open-label period. Placebo/etanercept patients achieved comparable results within 12 weeks that were sustained at 48 weeks (63%, 80%, and 73%, respectively). For the patients who initially received placebo, disease progression was inhibited once patients began receiving etanercept. Adverse effects were similar to the randomized phase.

A total of 618 patients with moderate to severe psoriasis were enrolled in a double-blind treatment with etanercept 50 mg twice weekly or placebo.<sup>263</sup> The primary endpoint, PASI 75 at week 12, was reached by 47% of the etanercept group and 5% of those receiving placebo ( $p < 0.0001$ ). Secondary endpoints were the functional assessment of chronic illness therapy fatigue (FACIT-F) scale and the Hamilton rating scale for depression (HAM-D). On the HAM-D evaluation, more patients receiving etanercept had at least a 50% improvement at week 12 compared with the placebo group. Fatigue was also improved in the etanercept group (mean FACIT-F improvement 5 versus 1.9;  $p < 0.0001$ ).

### ***golimumab (Simponi)***

GO-REVEAL: The safety and efficacy of golimumab were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 405 adult patients with moderately to severely active PsA ( $\geq 3$  swollen joints and  $\geq 3$  tender joints).<sup>264</sup> Patients in this study had a diagnosis of PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 centimeters in diameter. Prior treatment with a biologic TNF blocker was not allowed. Patients were randomly assigned to golimumab 50 mg ( $n = 146$ ), golimumab 100 mg ( $n = 146$ ), or placebo ( $n = 113$ ) given SC every 4 weeks. Patients were allowed to receive stable doses of concomitant methotrexate ( $\leq 25$  mg/week), low dose oral corticosteroids, and/or NSAIDs during the trial. The use of DMARDs, including sulfasalazine, hydroxychloroquine, cytotoxic agents, or other biologics, was prohibited. The primary endpoint was the percentage of patients achieving ACR 20 response at week 14 and was reported as: 51% (golimumab 50 mg), 45% (golimumab 100 mg) versus 9% (placebo), respectively ( $p < 0.001$  for all comparisons). Among secondary endpoints, 52% of patients administered golimumab 50 mg and 61% of patient receiving golimumab 100 mg, achieved ACR 20 at week 24 versus 12% in the placebo group ( $p < 0.001$ ). There was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower golimumab dose group (50 mg). ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant methotrexate. Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes. Golimumab 50 mg treatment also resulted in significantly greater improvement in enthesitis and skin manifestations in patients with PsA. Among the 74% of patients in whom at least 3% of the body surface area was affected by psoriasis at baseline, 40% of those in the golimumab 50 mg group

and 58% of those in the golimumab 100 mg group had at least 75% improvement in the PASI at week 14, compared with 3% of placebo-treated patients ( $p < 0.001$  for both doses). A 2-year follow-up of the GO-REVEAL trial indicated sustained responses at 2 years.<sup>265</sup> At week 104, patients originally randomized to golimumab 50 mg had an ACR 20 response of 67.1% and patients originally randomized to golimumab 100 mg had an ACR 20 response of 69.9%. Through week 104, 23 (6%) of patients discontinued golimumab because of an adverse event. Serious adverse events were reported for 16 (6.5%) and 18 (8%) of patients receiving golimumab 50 mg and 100 mg, respectively. There were 6 serious infections but, when assessed according to patient-years follow-up, no increase in the incidence of serous infection was observed for either golimumab arm. This analysis was, however, limited by the relatively short duration of placebo treatment and the small number of patients. No patient developed active TB through week 104, including the 44 patients who received TB prophylaxis secondary to detection of latent TB at time of trial participation screening. Eight patients were diagnosed with a malignancy during the 2-year time frame (1 colon cancer, 1 prostate cancer, 2 squamous cell lung cancers, and 4 basal cell carcinomas). When assessed by patient-years of follow-up, the incidence of malignancies for golimumab-treated patients was numerically higher compared to patients receiving placebo (95% CI, 0 to 0.74). Again, the authors note the analysis was limited by small sample size and the short period of placebo follow-up. When the number of malignancies (excluding the non melanoma skin cancers) in the trial were compared to the expected rates in the general U.S. population, the numbers were not statistically significantly different.

### ***infliximab (Remicade)***

IMPACT I, the Infliximab Multinational Psoriatic Arthritis Controlled Trial, was an investigator-initiated study of 104 patients with active PsA.<sup>266,267</sup> Patients received placebo or infliximab 5 mg/kg at weeks 0, 2, 6, and 14 with open-label infliximab 5 mg/kg every 8 weeks in follow-up. The primary endpoint, ACR 20 at week 16, was achieved in 69% of infliximab patients versus 8% on placebo ( $p < 0.001$ ). PASI 75 response in evaluable patients was 70.4% and 0% in the infliximab and placebo groups, respectively ( $p < 0.001$ ). At week 50, the same ACR 20 response was maintained.<sup>268</sup> No worsening of radiographic progression was noted in approximately 85% of the remaining patients. At week 98, 62% (48/78 patients) of infliximab-treated patients achieved an ACR 20 response.<sup>269</sup> Among patients with baseline PASI scores  $\geq 2.5$ , PASI 75 response was 64% (16/25 patients) at week 98. The average estimated annual radiographic progression with infliximab treatment was significantly reduced versus the estimated baseline rate of progression.

IMPACT II was a randomized, double-blind study of 200 patients with active PsA who had an inadequate response to DMARDs or NSAIDs.<sup>270</sup> Patients received infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 14, and 22. Significant improvements in both ACR 20 and PASI 75 were observed as early as week 2. At week 14, ACR 20 was seen in 58% (11% in placebo;  $p < 0.001$ ) and PASI 75 response in 64% (2% in placebo;  $p < 0.001$ ). The median PASI improvement in ACR 20 responders was 87.5%, whereas the median improvement in non-responders was 74%.<sup>271</sup> At week 24, 27% of infliximab-treated patients experienced ACR 70% versus 2% of placebo-treated patients ( $p < 0.001$ ). At week 24, 60% of infliximab-treated patients experienced PASI 75 versus 1% of placebo-treated patients, and 39% of infliximab-treated achieved PASI 90. There were similar numbers of adverse events in each group, although there were more serious adverse events in the infliximab group (8.7%) than in the placebo group (6.2%). In a continuation of the IMPACT II trial, infliximab therapy given every 8 weeks was continued for 1 year.<sup>272</sup> Placebo-assigned patients crossed over to infliximab at week 24. Patients randomized to infliximab who had no response or who lost response could escalate their dose to

10 mg/kg starting at week 38. Through 1 year of treatment, 58.9% and 61.4% of patients in the randomized infliximab and placebo/infliximab groups, respectively, achieved ACR 20; corresponding figures for PASI 75 were 50% and 60.3%. The safety profile of infliximab through week 54 was consistent with that seen through week 24. Two malignancies occurred: basal cell skin cancer (placebo) and stage I Hodgkin's lymphoma (infliximab). Radiographs of hands and feet were obtained at baseline and at weeks 24 and 54.<sup>273</sup> These were evaluated for erosions and joint space narrowing using the Sharp/van der Heijde scoring method modified for PsA. Radiographic progression, measured at week 24, was significantly less in patients initially randomized to infliximab compared with patients randomized to receive placebo ( $p < 0.001$ ). At week 54, slower radiographic progression was observed in patients on infliximab for 1 year compared to patients receiving infliximab for 24 weeks ( $p = 0.001$ ).

One hundred four patients with PsA in whom prior therapy with at least 1 DMARD had failed were recruited into an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled clinical trial.<sup>274</sup> During the initial blinded portion of the study, patients received infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, 6, and 14. After week 16, patients initially assigned to receive placebo crossed over to receive infliximab 5 mg/kg every 8 weeks through week 50, while patients initially randomized to infliximab continued to receive active treatment at the same dose through week 50. The proportion of infliximab-treated patients who achieved the primary endpoint of an ACR 20 response at week 16 (65%) was significantly higher than the proportion of placebo-treated patients who achieved the response (10%). In addition, 46% of infliximab-treated patients achieved an ACR 50 response and 29% achieved an ACR 70 response; no placebo-treated patient achieved these endpoints. Among patients who had PASI scores of  $\geq 2.5$  at baseline, 68% of infliximab-treated patients achieved improvement of at least 75% in the PASI score at week 16 compared with none of the placebo-treated patients. Continued therapy with infliximab resulted in sustained improvement in articular and dermatologic manifestations of PsA through week 50. The incidence of adverse events was similar between the treatment groups.

### **secukinumab (Cosentyx)**

A double-blind, phase 3, randomized clinical trial, the FUTURE 1 study, assessed the efficacy of secukinumab compared to placebo for the treatment of psoriatic arthritis in adults and active disease, as defined by  $> 3$  swollen and  $> 3$  tender joints despite NSAID, corticosteroid, or DMARD therapy ( $n = 606$ ).<sup>275,276</sup> Patients were randomly assigned 1:1:1 to placebo or IV secukinumab (10 mg/kg) at weeks 0, 2, and 4 followed by SC secukinumab at a dose of either 75 mg or 150 mg every 4 weeks. At week 16 or 24, patients assigned to placebo were switched to SC secukinumab 75 mg or 150 mg based on clinical response. The primary endpoint was ACR 20 at week 24. At 24 weeks, ACR 20 response was higher in both secukinumab groups (75 mg: 50.5%; 150 mg: 50%) compared to placebo (17.3%;  $p < 0.001$  for both). Secondary endpoints, such as ACR 50 and joint structural damage, were also superior in the secukinumab groups compared to placebo. At 52 weeks, the improvements were maintained. Adverse effects, specifically infections (e.g., candida), were more common in the secukinumab group. Four patients and 2 patients in the secukinumab groups had a stroke and myocardial infarction, respectively, while no patients in the placebo group experienced these events. This study was funded by the manufacturer of secukinumab and was used, in part, for FDA approval of this indication.

A second double-blind, phase 3, randomized clinical trial, the FUTURE 2 study, assessed the efficacy of secukinumab compared to placebo for the treatment of psoriatic arthritis in adults and active disease, as defined by  $> 3$  swollen and  $> 3$  tender joints despite NSAID, corticosteroid, or DMARD therapy

(n=397).<sup>277,278</sup> In both the FUTURE 1 and 2 trials, approximately 32% of patients had discontinued prior treatment with an anti-TNF $\alpha$  due to either intolerance or lack of efficacy, and approximately 55% were using concomitant methotrexate during the study. Patients were randomized 1:1:1:1 to secukinumab 75 mg, 150 mg, or 300 mg or placebo SC on weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks thereafter. At week 16 or 24, patients assigned to placebo were switched to SC secukinumab 75 mg or 150 mg based on clinical response. The primary endpoint was patients achieving ACR 20 at week 24. At week 24, 29% of patients using the 75 mg dose, 51% of patients using the 150 mg dose, and 54% of patients using the 300 mg dose compared to 15% of patients on placebo achieved ACR 20 (75 mg difference, 14% [95% CI, not reported]; 150 mg difference, 36% [95% CI, 24 to 48]; and 300 mg difference, 39% [95% CI, 27 to 51]). Significant differences from placebo were also seen with the 150 mg and 300 mg doses at weeks 16 and 24 in ACR 50 and ACR 70. Data with the 75 mg dose were not reported. No difference was seen in patients over both trials using concomitant methotrexate or those with prior anti-TNF $\alpha$  use.

### ***ustekinumab (Stelara)***

A total of 927 adult patients with active PsA ( $\geq 5$  swollen joints and  $\geq 5$  tender joints) were enrolled in 2 randomized, double-blind, placebo-controlled studies.<sup>279,280</sup> Patients in both trials had ongoing symptoms despite therapy with NSAIDs or DMARDs. In study 1 (PSUMMIT 1 trial), 615 patients were randomized to placebo, 45 mg SC ustekinumab, or 90 mg SC ustekinumab at weeks 0 and 4 and every 12 weeks thereafter. Patients with prior history of treatment with an anti-TNF inhibitor were excluded from this trial. Early escape was allowed at week 16 for patients on placebo or ustekinumab 45 mg if they had a less than 5% improvement from baseline in both tender and swollen joints. Primary efficacy endpoint was the proportion of patients with ACR 20 at week 24. A significantly higher proportion of patients in the ustekinumab groups than in the placebo group achieved an ACR 20 response at week 24 (difference in response rate 19.6% [95% CI, 10.8 to 28.5,  $p < 0.0001$ ] for the 45 mg group versus placebo and 26.7% [95% CI, 17.8 to 35.6,  $p < 0.0001$ ] for the 90 mg group versus placebo). ACR 20 treatment effects at week 24 were numerically lower for patients receiving concomitant methotrexate than for those patients who were not but tests of significance were not reported. The most common adverse events in the ustekinumab-treated patients were nasopharyngitis (4.6%), upper respiratory tract infection (3.4%), and headache (3.4%). In an open-label expansion study of the PSUMMIT 1 trial, clinical benefits were maintained through week 100.<sup>281</sup> In PsA Study 2 (n=312), the trial design was identical to the PSUMMIT 1 trial except PsA Study 2 included patients who had been previously treated with an anti-TNF agent (58% of study participants).<sup>282</sup> Seventy percent of the patients previously treated with an anti-TNF agent had discontinued their anti-TNF treatment for lack of efficacy or intolerance. The ACR 20 response at week 24 in this trial was 44% in patients receiving ustekinumab 45 mg, 44% in patients receiving ustekinumab 90 mg, and 20% for patients receiving placebo. Responses were similar in patients regardless of prior anti-TNF exposure.

## **Rheumatoid Arthritis**

### ***abatacept (Orencia)***

Patients with active RA despite therapy with methotrexate were randomized to receive, in addition to the methotrexate, abatacept 2 mg/kg, abatacept 10 mg/kg, or placebo for 6 months.<sup>283</sup> In the 339-patient study, those treated with the higher dose of abatacept were more likely to have an ACR 20 response than were patients who received placebo (60% and 35%, respectively;  $p < 0.001$ ). Significantly

higher rates of ACR 50 and ACR 70 responses were seen in both active treatment groups. Abatacept was well tolerated, with an overall safety profile similar to that of placebo.

Patients with active RA and an inadequate response to at least 3 months of anti-TNF $\alpha$  therapy were randomly assigned to receive abatacept (n=258) or placebo (n=133) every 2 weeks for 1 month, then every 4 weeks for 6 months.<sup>284</sup> Patients discontinued anti-TNF $\alpha$  therapy before randomization but were given at least 1 other DMARD. After 6 months, the rates of ACR 20 responses were 50.4% in the abatacept group and 19.5% in the placebo group ( $p<0.001$ ). The rates of ACR 50 and ACR 70 responses were also significantly higher in the abatacept group (20.3% and 10.2%, respectively) than in the placebo group (3.8 and 1.5%;  $p<0.003$  for both comparison). At 6 months, significantly more patients in the abatacept group (47.3%) had a clinically meaningful improvement from baseline in the Health Assessment Questionnaire Disability Index (placebo 23.3%;  $p<0.001$ ). The incidence of adverse events and serious infections were similar in each group.

Due to a lack of other data for therapy for 2 years with abatacept, this open-label extension study has been included. Patients completing the 6-month trial were eligible to enter the long-term open-label extension trial to evaluate the safety and efficacy of abatacept during 2 years of the ATTAIn (Abatacept Trial in Treatment of Anti-TNF INadequate responders) trial in patients with RA.<sup>285</sup> A total of 317 patients (218 from the abatacept and 99 from the placebo group) entered, and 222 (70%) completed 18 months of long-term extension treatment. The ACR 20 responses at 6 months and 2 years were 59.4 and 56.2%; ACR 50, 23.5 and 33.2%; ACR 70, 11.5 and 16.1%, respectively. Safety data were consistent with adverse effects reported in the 6-month trial.

In a double-blind study, 652 patients with active chronic RA despite treatment with methotrexate were randomized to abatacept (10 mg/kg) or placebo once monthly.<sup>286</sup> After 6 months in the abatacept in Inadequate Responders to methotrexate (AIM) study, ACR 20 (68% versus 40%), ACR 50 (40% versus 17%), and ACR 70 (20% versus 7%) responses occurred more frequently in the active treatment group than in the group receiving placebo ( $p<0.05$  for all comparisons). These differences were maintained at 1 year with ACR 20 (73% versus 40%), ACR 50 (48% versus 18%), and ACR 70 (29% versus 6%) responses, all occurring more frequently with abatacept ( $p<0.001$  for all comparisons). Physician function and progression of joint damage also favored abatacept. The incidence of adverse events was similar in both groups. There was, however, a higher incidence of infusion reactions with abatacept (8.8%) than with placebo (4.1%;  $p<0.05$ ). The manufacturer of abatacept, which also employs several of the authors, funded this study. At the end of 1 year, 539 patients remained.<sup>287</sup> Patients who received placebo for 1 year were switched to abatacept and followed for 1 additional year with 488 patients completing the 2 years of evaluation. After the second year, ACR 20 scores from year 2 were similar to year 1. Further inhibition of radiographic progression during year 2 of abatacept treatment was observed (57% reduction in mean change of total score in year 2 versus year 1;  $p<0.0001$ ), and minimal radiographic progression was observed (mean change in total score from baseline was 1.1 and 1.6 at year 1 and 2, respectively).<sup>288</sup>

The efficacy and safety of abatacept in methotrexate-naïve patients with early RA were investigated in a double-blind phase 3 study.<sup>289</sup> Patients had RA for less than 2 years and had a mean DAS28 of 6.3. Inclusion criteria also required patients to have erosions and be seropositive for rheumatoid factor and/or anti-CCP2 that are associated with poor radiologic outcomes. Patients were randomized to abatacept 10 mg/kg plus methotrexate (n=256) or placebo plus methotrexate (n=253). The co-primary endpoints were the portion of patients achieving disease activity score in 28 joints (DAS-28)-defined remission and joint damage progression measured by Genant-modified Sharp total score at 1 year.

After 1 year, a significantly greater proportion of abatacept plus methotrexate-treated patients achieved remission (41.4% versus 23.3%;  $p < 0.001$ ). Less radiographic progression occurred in the combination treatment group (mean change in total Sharp score, 0.63 versus 1.06;  $p = 0.04$ ). Adverse effects were comparable between groups for frequency of adverse effects, serious adverse events, serious infections, and malignancies.

The efficacy and safety of abatacept administered subcutaneously (SC) in 1,457 RA patients who had an inadequate response to methotrexate was studied in a randomized, double-blind, double-dummy, non-inferiority study (Study SC-I).<sup>290</sup> Patients were randomized with stratification by body weight (< 60 kg, 60 to 100 kg, > 100 kg) to receive abatacept 125 mg SC injections weekly, after a single IV loading dose of abatacept based on body weight or abatacept IV on days 1, 15, 29, and every 4 weeks thereafter. Patients continued taking their current dose of methotrexate from the day of randomization. The main outcome measure was ACR 20 at 6 months. The pre-specified non-inferiority margin was a treatment difference of -7.5%. The percentage of patients achieving ACR response in the abatacept SC and IV treatment arms at 6 months was as follows: ACR 20 (76% SC, 76% IV); ACR 50 (52% SC, 50% IV); ACR 70 (26% SC, 25% IV). Non-inferiority of abatacept SC relative to IV infusions of abatacept with respect to ACR 20 responses up to 6 months of treatment was demonstrated. No major differences in ACR responses were observed between IV and SC treatment groups in subgroups based on weight categories.

#### ***abatacept (Orencia) versus infliximab (Remicade)***

A double-blind trial compared the efficacy and safety of abatacept and infliximab in 431 adults with RA.<sup>291</sup> Patients were randomized to abatacept approximately 10 mg/kg every 4 weeks ( $n = 156$ ), infliximab 3 mg/kg every 8 weeks ( $n = 165$ ), placebo every 4 weeks ( $n = 110$ ), and background methotrexate. The primary objective of the study was to evaluate the mean change from baseline in Disease Activity Score (based on erythrocyte sedimentation rates; DAS28 [ESR]) for the abatacept versus placebo groups at day 197. At 6 months, mean changes in DAS28 (ESR) were significantly greater for abatacept versus placebo (-2.53 versus -1.48;  $p < 0.001$ ) and infliximab versus placebo (-2.25 versus -1.48;  $p < 0.001$ ). At day 197, ACR 20 responses were significantly greater with abatacept versus placebo (ACR 20, 66.7% versus 41.8%;  $p < 0.001$ ). ACR 20 responses were also significantly higher in the infliximab group versus placebo (ACR 20, 59.4% versus 41.8%;  $p = 0.006$ ). For abatacept versus infliximab treatment at day 365, reductions in the DAS28 (ESR) were -2.88 versus -2.25. At day 365, the ACR 20 response rates were 72.4% for abatacept and 55.8% for infliximab. The DAS28-defined remission rates were 18.7% and 12.2% for abatacept and infliximab, respectively. Adverse events and discontinuations related to adverse events were lower with abatacept than infliximab. The manufacturer of abatacept funded the study.

#### ***abatacept (Orencia) versus adalimumab (Humira)***

AMPLE (Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate) was a phase 3, randomized, prospective study.<sup>292</sup> Patients with active RA ( $n = 646$ ) who had never received a biologic agent and had an inadequate response to methotrexate were randomized to abatacept 125 mg SC weekly or adalimumab 40 SC biweekly, both given in combination with methotrexate for the 2-year study period. Patients were not blinded, but the independent clinical assessors, as well as the radiologists interpreting the radiographs, were blinded with regard to each patient's treatment. The primary endpoint was treatment inferiority based on ACR 20 at 1 year. Other comparisons measured were radiographic response (of the hands and feet taken at baseline and on

day 365), as well as overall safety. At 1 year, 274 (86.2%) of the abatacept-treated patients and 269 (82%) of the adalimumab-treated patients completed the study. The main reasons for discontinuation were lack of efficacy (3.8% of abatacept-treated patients versus 4.6% of adalimumab-treated patients) and adverse events (3.5% of abatacept-treated patients versus 6.1% of adalimumab-treated patients). The proportion of patients achieving an ACR 20 response at 1 year was 64.8% (95% CI, 59.5% to 70%) in the abatacept group and 63.4% (95% CI, 58.2% to 68.6%) in the adalimumab group. The difference in ACR 20 response rates between groups was 1.1% (95% CI, -6.5% to 8.7%), demonstrating noninferiority of abatacept compared to adalimumab. The rate of radiographic non-progression from baseline to 1 year was observed to be 84.8% in the abatacept group and 88.6% in the adalimumab group (difference between groups was 4.1% (95% CI, -1.5% to 9.6%). The rate of serious adverse events was 10.1% in the abatacept group and 9.1% in the adalimumab group. Discontinuations due to adverse effects occurred at almost twice the rate in the adalimumab group (6.1%) than in the abatacept group (3.5%). The incidences of infection (63.2% versus 61.3%) and malignancies (1.6% versus 1.2%) were similar between the 2 groups; however, the rate of autoimmune events was higher in the abatacept group (3.1%) compared to the adalimumab group (1.2%). Statistical analyses were not reported on these safety measures. Local injection site reactions occurred in significantly fewer patients in the abatacept group than in the adalimumab group (3.8% versus 9.1%; 95% CI, -9.13 to -1.62;  $p=0.006$ ). A follow-up publication reported 79.2% of abatacept and 74.7% of adalimumab patients completed year 2 of the AMPLE trial. At year 2, efficacy outcomes, including radiographic results, remained comparable between groups and with year 1 results. The ACR 20 at year 2 was 59.7% for abatacept and 60.1% for adalimumab. Overall, the rates of adverse events and serious adverse events were similar between the 2 groups; however, there were more serious infections with adalimumab (3.8% versus 5.8%), including 2 cases of tuberculosis with adalimumab. There were fewer discontinuations due to adverse events (3.8% versus 9.5%) or serious adverse events (1.6% versus 4.9%) in the abatacept group. Injection site reactions occurred less frequently with abatacept (4.1% versus 10.4%).<sup>293</sup>

### ***adalimumab (Humira) with methotrexate versus placebo + methotrexate***

The Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Rheumatoid Arthritis (ARMADA) trial was a 24-week, double-blind study of 271 patients with active RA despite treatment with methotrexate.<sup>294</sup> Patients were randomly assigned to receive adalimumab 20, 40, or 80 mg or placebo SC every other week while continuing to take their long-term stable dosage of methotrexate. The proportion of patients achieving ACR 20 at 24 weeks was significantly greater in the adalimumab 20 mg (47.8 %), 40 mg (67.2%), and 80 mg (65.8%) groups than in the placebo group (14.5%;  $p<0.001$  for all comparisons with placebo). Most patients receiving adalimumab achieved an ACR 20 response at week 1. Compared with the ACR 50 response rate of 8.1% in the placebo group, ACR 50 response rates were higher in the groups receiving adalimumab 20 mg (31.9%  $p=0.003$ ), 40 mg (55.2%;  $p<0.001$ ), and 80 mg (42.5%;  $p<0.001$ ). Near-remission, defined as an ACR 70 response rate, occurred in 4.8% of the placebo group ( $p<0.001$ ), 10.1% of the 20 mg group ( $p=NS$ ), 26.9% of the 40 mg group ( $p<0.001$ ), and 19.2% of the 80 mg group ( $p=0.02$ ). The incidence of adverse events was similar in all groups.

A randomized trial of adalimumab evaluated 619 patients with active RA who had average disease duration of more than 10 years and who had inadequate response to methotrexate.<sup>295</sup> Patients received adalimumab 40 mg every other week, 20 mg every week, or placebo. All patients received stable doses of methotrexate. The primary efficacy endpoints were radiographic progression at week 52 (total Sharp score by a modified method [TSS]), clinical response at week 24 (ACR 20), and physical function at week 52 (HAQ-DI). Radiographs were assessed using a modified version of the Sharp

method. Digitized images were scored by physicians who were blinded to the treatment, chronological order, and clinical response of each patient. Erosion scores were recorded for each hand/wrist and each forefoot on a 6-point scale (0 = no erosions; 1 = 1 discrete erosion or  $\leq 20\%$  joint involvement; 2 = 2 separate quadrants with erosion or 21 to 40% joint involvement; 3 = 3 separate quadrants with erosion or 41 to 60% joint involvement; 4 = all 4 quadrants with erosion or 61 to 80% joint involvement; and 5 = extensive destruction with  $> 80\%$  joint involvement). Joint space narrowing scores were recorded for each hand/wrist and each forefoot on a 5-point scale (0 = no narrowing; 1 = up to 25% narrowing; 2 = 26 to 65% narrowing; 3 = 66 to 99% narrowing; and 4 = complete narrowing). To determine the modified TSS for each patient, the total erosion score (scale 0 to 230) and the joint space narrowing score (scale 0 to 168) were added (TSS scale 0 to 398). At weeks 24 and 52, adalimumab-treated patients had significantly less disease progression than placebo-treated patients. Patients receiving adalimumab plus methotrexate experienced significantly less radiographic progression than those taking methotrexate only ( $p \leq 0.001$ ). At week 52, no new erosions were observed in significantly more patients receiving adalimumab 40 mg every other week (61.8%) than in those taking placebo (46%). In addition, joint erosion scores improved in almost twice as many patients receiving adalimumab 40 mg every other week than placebo (38.2% versus 19.3%, respectively). At 52 weeks, ACR 20 responses were achieved by 59% of patients receiving adalimumab 40 mg every other week (placebo 24%) and ACR 50 responses were achieved by 41.5% (placebo 9.5%). ACR 70 was achieved by 23.2% of patients treated with adalimumab 40 mg every other week compared to 4.5% in the placebo group. Physical function improved significantly more for patients receiving adalimumab 40 mg every other week than for patients on placebo ( $p \leq 0.001$ ). The rate of adverse events was similar among patients treated with adalimumab and placebo, although the proportion of patients reporting serious infections was higher in patients receiving adalimumab (3.8%) than placebo (0.5%;  $p \leq 0.002$ ). The most common adverse events occurring in adalimumab 40 mg and placebo-treated patients, respectively, included injection-site reaction (26.1% versus 24%), upper-respiratory infection (19.8% versus 13.5%), rhinitis (16.4% versus 16.5%), and sinusitis (15.9% versus 13%). Forty-two adalimumab patients and 13 placebo patients withdrew from the study due to adverse events.

A double-blind study enrolled 799 patients with RA with active disease of less than 3 years duration to compare the efficacy and safety of adalimumab plus methotrexate versus either monotherapy over 2 years – the PREMIER study.<sup>296</sup> Patients had previously not received methotrexate. Patients were randomized to adalimumab 40 mg every other week plus methotrexate or either monotherapy. Co-primary endpoints at year 1 were ACR 50 and mean change from baseline in the modified TSS. The combination therapy had a superior ACR 50 response at 1 year (62%) compared to those receiving methotrexate (46%) or adalimumab monotherapy (41%; both  $p < 0.001$ ). The combination group had less radiographic progression ( $p \leq 0.002$ ), as measured by the modified TSS, at both year 1 and 2 than patients on methotrexate and adalimumab monotherapy. Adverse events were similar in all groups.

### ***adalimumab (Humira) in DMARD-nonresponders***

In a 26-week, double-blind, placebo-controlled trial, 544 patients with RA who had failed therapy with other DMARDs were randomized to monotherapy with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly, or placebo.<sup>297</sup> After 26 weeks, patients treated with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, and 40 mg weekly had significantly better response rates than those treated with placebo: ACR 20 (35.8%, 39.3%, 46%, and 53.4%, respectively versus 19.1%;  $p \leq 0.01$ ); ACR 50 (18.9%, 20.5%, 22.1%, and 35% versus 8.2%;  $p \leq 0.05$ ); ACR 70 (8.5%, 9.8%, 12.4%, and 18.4% versus 1.8%;  $p \leq 0.05$ ). Patients treated with

adalimumab achieved better improvements in HAQ DI scores than those receiving placebo ( $p \leq 0.01$  for all comparisons). There were no significant differences between treatment groups in the occurrence of serious adverse events, serious infections, or malignancies. Injection site reaction occurred in 10.6 and 0.9% of adalimumab- and placebo-treated patients, respectively ( $p \leq 0.05$ ).

### ***anakinra (Kineret)***

In a 24-week extension of a 24-week, randomized, double-blind study of anakinra in 472 patients with RA, patients who had received placebo were randomized to receive anakinra 30 mg, 75 mg, or 150 mg SC daily.<sup>298</sup> Patients who had been initially randomized to 1 of the 3 anakinra dosages continued to receive the same dosage. Radiographs of the hands were obtained at baseline and at 24 and 48 weeks. The radiographs were evaluated using a modified TSS. The mean change in the modified TSS of 178 patients who completed 48 weeks treatment with active drug was significantly less than the change observed in the 58 patients who received placebo for 24 weeks and anakinra for 24 weeks ( $p=0.015$ ). Significant reductions in the second 24-week period were observed in patients receiving anakinra 75 mg/day ( $p=0.006$ ) and 150 mg/day ( $p=0.008$ ). The modified TSS was reduced significantly more during the second 24-week treatment period compared to the first ( $p<0.001$ ).

### ***anakinra (Kineret) and etanercept (Enbrel) combination therapy***

Two hundred forty-four patients in whom RA was active despite methotrexate therapy were treated with etanercept 25 SC mg twice weekly, etanercept 25 mg SC twice weekly plus anakinra 100 mg daily, or etanercept 25 mg SC once weekly plus anakinra 100 mg daily for 6 months in a double-blind multicenter study.<sup>299</sup> Patients were naïve to anticytokine therapy. Thirty-one percent of the patients treated with twice weekly etanercept plus anakinra achieved an ACR 50 response, compared with 41% of the patients treated with etanercept only ( $p=NS$ ). The incidence of serious infections (0% for etanercept alone and 3.7% to 7.4% for combination therapy), injection-site reactions, and neutropenia was increased with combination therapy.

### ***anakinra (Kineret) with methotrexate versus placebo + methotrexate***

A total of 419 patients with moderate to severe active RA, despite at least 6 months of methotrexate therapy, received either placebo or anakinra 0.04 to 2 mg/kg SC daily in addition to methotrexate.<sup>300</sup> At 12 weeks, the proportion of patients who achieved an ACR 20 response was significantly higher among those who received anakinra 1 mg/kg (46%;  $p=0.001$ ) and 2 mg/kg (38%;  $p=0.007$ ) than among those who received placebo (19%). At 24 weeks, the percentage of responders remained significantly higher among anakinra 1 mg/kg recipients (42%) than among placebo recipients (23%;  $p=0.004$ ). Similar improvements in anakinra-treated subjects were noted in individual ACR components, onset of ACR 20 response, sustainability of ACR 20 response, and magnitude of ACR response. This study was supported by a grant from the manufacturers of anakinra.

In a double-blind study, 506 patients with active RA despite treatment with methotrexate were randomized to receive anakinra 100 mg or placebo SC daily in addition to continued treatment with methotrexate.<sup>301</sup> At the first study assessment (4 weeks), twice as many patients achieved an ACR 20 response with anakinra as with placebo ( $p<0.005$ ). The primary outcome, ACR 20 at week 24, was achieved by 38% of the anakinra group and by 22% of the placebo group ( $p<0.001$ ). A greater proportion of patients treated with anakinra also achieved ACR 50 (17% versus 8%;  $p<0.01$ ) and ACR 70 (6% versus 2%;  $p<0.05$ ) responses. Compared with placebo, anakinra also resulted in significant responses in individual components of the ACR response, pain, CRP levels, and ESR. The safety profile

for anakinra was similar to placebo, except for more frequent mild-to-moderate injection site reactions (65% versus 24%). The manufacturer of anakinra supported the study.

### ***certolizumab pegol (Cimzia) versus placebo***

The FAST4WARD (eFficAcY and Safety of cerTolizumab pegol – 4 Weekly dosAge in Rheumatoid arthritis) study was a 24-week, multicenter, double-blind trial that evaluated the efficacy and safety of certolizumab pegol as monotherapy in patients with active RA.<sup>302</sup> Patients who had not received a biologic therapy for RA within 6 months and had previously failed at least 1 DMARD (n=220) were randomized 1:1 to receive certolizumab pegol 400 mg or placebo every 4 weeks. ACR 20 response at week 24, the primary endpoint, was 45.5% for certolizumab pegol and 9.3% for placebo ( $p<0.001$ ). Most adverse events in both groups were mild or moderate. There were no reports of tuberculosis, opportunistic infections, malignancy, demyelinating disease, or congestive heart failure in either group. However, 2 cases (1.8%) of serious infection and 2 cases (1.8%) of benign tumors were reported in the certolizumab pegol group. This study was funded by the manufacturer of certolizumab pegol.

### ***certolizumab pegol (Cimzia) + methotrexate versus methotrexate monotherapy***

RAPID 2 was a 24-week, phase 3, multicenter, double-blind study that evaluated the efficacy and safety of subcutaneous certolizumab pegol plus methotrexate compared with placebo plus methotrexate.<sup>303</sup> Patients (n=619) with active adult-onset RA were randomized 2:2:1 to certolizumab pegol 400 mg at weeks 0, 2, and 4 followed by 200 mg or 400 mg plus methotrexate, or placebo plus methotrexate, every 2 weeks for 24 weeks. The primary endpoint, ACR 20 response at week 24, was achieved by 57.3% of the low-dose certolizumab pegol group, 57.6% of the high-dose certolizumab pegol group, and 8.7% of the placebo-treated group ( $p\leq0.001$ ). Certolizumab pegol low- and high-dose groups also significantly inhibited radiographic progression; mean changes from baseline in mTSS at week 24 were 0.2 and -0.4, respectively, versus 1.2 for placebo (rank analysis  $p\leq0.01$ ). Physical function improved rapidly with certolizumab pegol compared to placebo based on mean changes from baseline in HAQ-DI at week 24 ( $p\leq0.001$ ). Most adverse events were mild or moderate, with low incidence of withdrawals due to adverse events. Five patients treated with certolizumab pegol developed tuberculosis. The RAPID 2 study was fully funded by the manufacturer of certolizumab pegol.

Certolizumab pegol plus methotrexate and placebo plus methotrexate were compared in 982 patients with active RA with an inadequate response to methotrexate therapy alone.<sup>304</sup> The 52-week, phase 3, randomized, double-blind trial evaluated ACR 20 response rates at week 24 and the mean change from baseline in the modified total Sharp score at week 52. Certolizumab pegol was given as an initial dosage of 400 mg at weeks 0, 2, and 4, with a subsequent dosage of 200 mg or 400 mg given every 2 weeks, plus methotrexate, or placebo plus methotrexate. At week 24, ACR 20 response rates using nonresponder imputation for the certolizumab pegol 200 mg and 400 mg groups were 58.8% and 60.8%, respectively, as compared with 13.6% for the placebo group. Differences in ACR 20 response rates versus placebo were significant at week 1 and were sustained to week 52 ( $p<0.001$ ). At week 52, mean radiographic progression from baseline was reduced in patients treated with certolizumab pegol 200 mg (0.4 Sharp units) or 400 mg (0.2 Sharp units) as compared with that in placebo-treated patients (2.8 Sharp units) ( $p<0.001$  by rank analysis). Adverse effects were mild or moderate.

### ***etanercept (Enbrel) + methotrexate versus methotrexate monotherapy***

The combination of methotrexate and etanercept in active early RA (COMET) study compared remission and radiographic non-progression in patients treated with methotrexate monotherapy or

combination of etanercept with methotrexate.<sup>305</sup> A total of 542 methotrexate-naïve patients with early moderate-to-severe rheumatoid arthritis for 3 to 24 months were randomized to methotrexate monotherapy (n=268) titrated up from 7.5 mg per week to a maximum of 20 mg per week by week 8 or methotrexate with the same titration schedule plus etanercept 50 mg weekly (n=274). In the double-blind study, remission was measured with the disease activity score in 28 joints (DAS28) and radiographic non-progression measured with modified total Sharp score. Fifty percent of patients on combination therapy achieved clinical remission compared to 28% receiving methotrexate monotherapy (effect difference, 22.05%; 95% CI, 13.96 to 30.15; p<0.0001). The manufacturer of etanercept funded the study.

The COMET study continued to evaluate the outcomes of patients who completed the first year of the 2 year study.<sup>306</sup> The original combinations group either continued etanercept plus methotrexate (n=111) or received etanercept monotherapy (n=111) in year 2. The original methotrexate group received either methotrexate plus etanercept (n=90) or continued methotrexate monotherapy (n=99) in year 2. Efficacy endpoints were DAS28 remission and radiographic nonprogression at year 2. DAS28 remission was achieved by 62/108 patients of the etanercept plus methotrexate group continuous group, 54/108 patients for the etanercept plus methotrexate group then switched to etanercept only, 51/88 patients of the methotrexate group switched to combination therapy, and 33/94 patients in the methotrexate monotherapy group (p<0.01 for the etanercept plus methotrexate for 2-year group, and methotrexate monotherapy for year 1 then combination therapy for year 2 versus the methotrexate monotherapy for 2-years group). The proportions of subjects achieving radiographic nonprogression (n=360) were 89/99 of the combination therapy over 2 years group, 74/99 of the combination therapy then etanercept monotherapy group, 59/79 methotrexate then combination therapy group, and 56/83 methotrexate monotherapy over 2-years group (p<0.01 versus each of the other groups). No new safety issues or differences in serious adverse events were reported.

#### ***etanercept (Enbrel) + methotrexate versus methotrexate monotherapy versus etanercept monotherapy***

The TEMPO study evaluated the combination of etanercept plus methotrexate versus each of the single treatments in 686 patients with RA.<sup>307</sup> In the double-blind study, patients were randomized to etanercept 25 mg twice weekly, oral methotrexate up to 25 mg weekly or the combination. In the 682 patients that received study drug, the combination was more efficacious than methotrexate or etanercept alone in retardation of joint damage over 52 weeks (mean total Sharp score, -0.54 [95% CI, -1 to -0.07] versus 2.8 [95% CI, 1.08 to 4.51; p<0.0001] and 0.52 [95% CI, -0.1 to 1.15; p=0.0006], respectively). The primary efficacy endpoint was the numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks. ACR-N AUC at 24 weeks was greater for the combination group compared with etanercept alone and methotrexate alone (18.3%-years [95% CI, 17.1 to 19.6] versus 14.7%-years [13.5 to 16; p<0.0001] and 12.2%-years [95% CI, 11 to 13.4; p<0.0001], respectively). The mean difference in ACR-N AUC between combination and methotrexate alone was 6.1 (95% CI, 4.5 to 7.8; p<0.0001) and between etanercept and methotrexate was 2.5 (95% CI, 0.8 to 4.2; p=0.0034). To evaluate the clinical response between 12 and 24 weeks in subjects with RA, 12-week non-responders from the above TEMPO study were assessed at 24 weeks according to ACR response criteria. The proportion of subjects who successfully maintained response to 52 weeks was analyzed as were radiographic outcomes. Over 80% of the week 24 ACR 20/50/70 responders in the etanercept plus methotrexate arm sustained their response to 52 weeks.<sup>308</sup> In the etanercept arms,

a delayed clinical response was not associated with increased radiographic progression at week 52. The number of patients reporting infections or adverse events was similar in all groups.

### ***golimumab (Simponi) subcutaneous***

**GO-AFTER:** This was a phase 3, multicenter, double-blind trial that included 461 patients with moderately to severely active rheumatoid arthritis who had previously received TNF- $\alpha$  therapy.<sup>309</sup> Eligible patients had been treated with at least 1 dose of a TNF $\alpha$  inhibitor previously. Patients continued stable doses of methotrexate, sulfasalazine, hydroxychloroquine, oral corticosteroids, and NSAIDs. Patients were randomized to receive subcutaneous injections of placebo (n=155), 50 mg golimumab (n=153), or 100 mg golimumab (n=153) every 4 weeks. The primary endpoint was achievement of ACR 20 at week 14. At week 16, patients who did not achieve ACR 20 were given rescue therapy and changed treatment from placebo to 50 mg golimumab, or from 50 mg to 100 mg golimumab. At week 14, 18% of patients on placebo, 35% of patients on 50 mg golimumab (odds ratio [OR], 2.5; 95% CI, 1.5 to 4.2; p=0.0006), and 38% of patients on 100 mg golimumab (OR, 2.8; 95% CI, 1.6 to 4.7; p=0.0001) achieved ACR 20. Serious adverse events were recorded in 7% of patients on placebo, 5% on 50 mg golimumab, and 3% on 100 mg golimumab.

**GO-FORWARD:** This was a phase 3, multicenter, double-blind, placebo controlled-trial.<sup>310</sup> All patients were diagnosed with moderate to severe RA and had been on a stable methotrexate dose of 15 to 25 mg/week immediately prior to screening. Patients (n=444) were randomized to receive placebo plus methotrexate, golimumab 100 mg SC plus placebo, golimumab 50 mg SC plus methotrexate, or golimumab 100 mg SC plus methotrexate every 4 weeks. Primary endpoints were proportion of patients that achieved ACR 20 at week 14 and the change from baseline in the HAQ-DI at week 24. The proportion of patients who achieved an ACR 20 response at week 14 was 33.1% in the placebo/methotrexate group, 44.4% (p=0.059) in the golimumab 100 mg/placebo group, 55.1% (p=0.001) in the golimumab 50 mg/methotrexate group and 56.2% (p<0.001) in the golimumab 100 mg/methotrexate group. At week 24, median improvements from baseline in HAQ-DI scores were 0.13, 0.13 (p=0.24), 0.38 (p<0.001), and 0.5 (p<0.001), respectively. At week 52, the ACR 20 response rates were 44% for the placebo/methotrexate group, 45% for the golimumab 100 mg plus placebo, 64% for the golimumab 50 mg/methotrexate, and 58% for the golimumab 100 mg/methotrexate group.<sup>311</sup> The golimumab 100 mg/methotrexate group had a higher rate of serious adverse effects and infections. A 2-year follow-up of this trial reported that 392 patients continued from week 52 through week 104. Clinical improvement was maintained through week 104; 75% of golimumab 50 mg + methotrexate patients achieved an ACR 20 response and 72% of patients randomized to golimumab 100 mg + methotrexate achieved an ACR 20 response. Incidences of serious infections were 2.24, 4.77, and 5.78 per 100 patient-years of follow-up for golimumab 50 mg + methotrexate, golimumab 100 mg + placebo, and 100 mg + methotrexate, respectively.<sup>312</sup>

**GO-BEFORE:** This study evaluated 637 patients with moderately to severely active RA who were methotrexate-naïve and had not previously been treated with a biologic TNF blocker.<sup>313,314</sup> Patients were randomized to receive methotrexate, golimumab 50 mg SC plus methotrexate, golimumab 100 mg SC plus methotrexate, or golimumab 100 mg SC monotherapy. For patients receiving methotrexate, the methotrexate dose was 10 mg per week beginning at week 0 and increased to 20 mg per week by week 8. Golimumab dose or placebo was administered every 4 weeks. The use of other DMARDs or other biologics was prohibited. The primary endpoint was the percentage of patients achieving an ACR 50 response at week 24. The combination groups of golimumab 50 mg or 100 mg plus methotrexate in the intent-to-treat population did not show a significant difference on proportion of patients achieving

ACR 50 response from the placebo plus methotrexate group (38.4% and 29.4%, respectively;  $p=0.053$ ). When 3 untreated patients were excluded in a post-hoc modified ITT analysis, the ACR 50 response showed statistically significant differences between the combined group and placebo plus methotrexate (38.5% versus 29.4%;  $p=0.049$ ) and between golimumab 50 mg plus methotrexate (40.5%;  $p=0.038$ ) but not golimumab 100 mg plus methotrexate (36.5%;  $p=0.177$ ) and placebo plus methotrexate. Golimumab 100 mg plus placebo was non inferior to placebo plus methotrexate for the ACR 50 response at week 24 (33.1%; 95% CI, -5.2% to -10%). The combination of golimumab plus methotrexate demonstrated a significantly better response compared with placebo plus methotrexate in most other efficacy parameters, including response/remission, according to the Disease Activity Score in 28 joints.

In a multicenter, double-blind, randomized controlled trial, golimumab was evaluated in 172 patients with RA despite treatment with methotrexate.<sup>315</sup> Patients were randomized to 1 of 5 treatment arms: placebo plus methotrexate, golimumab 50 mg or 100 mg every 2 or 4 weeks plus methotrexate through week 48. Patients originally assigned to receive injections every 2 weeks had the interval increased to every 4 weeks starting at week 20. Patients assigned to the placebo group were given infliximab 3 mg/kg at weeks 20, 22 and 28 and then every 8 weeks. methotrexate doses were stable throughout the study period. Seventy-five percent of patients completed the study. The primary endpoint was the proportion of patients achieving an ACR 20 response at week 16. The ACR 20 response rates at week 16 were 37.1% for placebo + methotrexate group, 50% for golimumab 50 mg every 2 weeks + methotrexate, 60% for golimumab 50 mg every 4 weeks + methotrexate, 79.4% for golimumab 100 mg every 2 weeks + methotrexate ( $p<0.001$  versus placebo), and 55.9% for golimumab 100 mg every 4 weeks + methotrexate. At week 20, patients who had been receiving golimumab injections every 2 weeks switched to injections every 4 weeks without an appreciable decrease in the proportion of ACR 20 responders. The patients on golimumab 100 mg + methotrexate had increased injection site reactions (36.1%) compared to the placebo group (11.8%). Three serious infections were reported in the golimumab groups compared to 2 serious infections reported in those patients who received infliximab after week 20.

#### ***golimumab (Simponi Aria) intravenous + methotrexate versus placebo + methotrexate***

GO FURTHER was a 24-week randomized, double-blind, placebo-controlled, multicenter, phase 3 trial.<sup>316</sup> Patients ( $n=592$ ) 18 years of age and older with moderately to severely active RA despite concurrent methotrexate therapy and had not previously been treated with a biological TNF blocker. Patients were diagnosed by the ACR criteria and had at least 6 swollen and 6 tender joints. Patients were randomized 2:1 to receive golimumab 2 mg/kg IV at weeks 0, 4, and every 8 weeks thereafter ( $n=395$ ) in addition to methotrexate (15 to 25 mg/kg) or placebo ( $n=197$ ) in addition to methotrexate (15 to 25 mg/kg). Both groups had similar baseline demographics and 81% were women and 80% were Caucasian. The primary endpoint of the trial was the percentage of patients achieving a 20% ACR improvement by week 14. At week 14, 231 of 395 (58.5%) patients in the golimumab + methotrexate group and 49 of 197 (24.9%) patients in the placebo + methotrexate group achieved a 20% ACR improvement (95% CI, 25.9 to 41.4;  $p<0.001$ ). The most common adverse effects at week 14 were infections and infestations with 24.3% in the golimumab and 20.8% in the placebo group. In an open-label expansion study, clinical response with golimumab + methotrexate was maintained through week 100.<sup>317</sup>

### ***infliximab (Remicade)***

The BeST study compared clinical and radiographic outcomes of 4 different treatment strategies in a multicenter, randomized clinical trial.<sup>318</sup> Treatment strategies were DMARD monotherapy, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, and initial combination therapy with infliximab. Treatment adjustments were done every 3 months. For patients with early RA, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy. After 5 years, initial combination therapy resulted in significantly less joint damage progression, reflecting the earlier clinical response.<sup>319</sup>

### ***infliximab (Remicade) with methotrexate versus placebo + methotrexate***

One thousand forty-nine RA patients with active disease and no prior treatment with methotrexate or TNF $\alpha$  inhibitor were randomized to 1 of 3 treatment groups: methotrexate + placebo, methotrexate + infliximab 3 mg/kg, and methotrexate + infliximab 6 mg/kg.<sup>320</sup> Methotrexate dosages were rapidly escalated to 20 mg/week and infliximab or placebo infusions were given at weeks 0, 2, 6, and every 8 weeks thereafter through week 46. At week 54, the median percentage of improvement in ACR scores was higher for the methotrexate + infliximab 3 mg/kg (38.9%) and methotrexate + infliximab 6 mg/kg (46.7%) groups than for the methotrexate + placebo group (26.4%;  $p < 0.001$  for both comparisons). Patients in the methotrexate + infliximab 3 mg/kg and methotrexate + infliximab 6 mg/kg groups also showed less radiographic progression at week 54, as measured by modified TSS, than those receiving methotrexate alone ( $p < 0.001$  for each comparison). Methotrexate + placebo halted radiographic progression only if patients achieved remission within 3 months, whereas methotrexate + infliximab halted or minimized progression in patients with low or moderate activity, respectively.<sup>321</sup> Physical function improved significantly more in the methotrexate + infliximab 3 mg/kg and methotrexate + infliximab 6 mg/kg groups than in the methotrexate + placebo group. Infliximab therapy was associated with a significantly higher incidence of serious infections, especially pneumonia.

In ATTRACT (Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy), a double-blind trial, 428 patients with active RA and who had received methotrexate for at least 3 months at a stable dose for at least 4 weeks were randomized to placebo or 1 of 4 regimens of infliximab at weeks 0, 2, and 6, then every 4 or 8 weeks thereafter.<sup>322</sup> At 30 weeks, ACR 20 was achieved in 50% to 60% of patients receiving infliximab compared with 20% of patients receiving placebo ( $p < 0.001$  for each of the infliximab dosage regimens compared to placebo). ACR 50 was achieved in 26 to 31% of infliximab patients compared to 5% of patients on placebo ( $p < 0.001$ ). Infliximab was well tolerated with no more withdrawals for adverse events or serious adverse events or infections than in the placebo group.

To evaluate the efficacy and safety of repeated administration of infliximab plus methotrexate over a 2-year period in patients with RA who previously experienced an incomplete response to methotrexate, 428 such patients were randomly assigned to receive methotrexate plus infliximab 3 or 10 mg/kg or placebo for 54 weeks with an additional year of follow-up.<sup>323</sup> The protocol was later amended to allow for continued treatment during the second year. Of 259 patients who entered the second year of treatment, 216 continued to receive infliximab plus methotrexate for 102 weeks. Ninety-four of these 259 patients experienced a gap in therapy of more than 8 weeks before continuing therapy. Infusions were administered at weeks 0, 2, and 6 followed by treatment every 4 weeks or every 8 weeks at a dose of 3 or 10 mg/kg for a total of 102 weeks (including the gap in therapy). The infliximab plus methotrexate regimens resulted in significantly greater improvement in

physical function and quality-of-life physical component scores compared with the methotrexate-only group. There also was stability in the quality-of-life mental component summary score among patients who received the infliximab plus methotrexate regimens. The proportion of patients achieving an ACR 20 response at week 102 varied from 40% to 48% for the infliximab plus methotrexate groups compared with 16% for the methotrexate-only group.

### ***tocilizumab (Actemra) intravenous***

The double-blind, parallel-group AMBITION study evaluated the efficacy and safety of tocilizumab monotherapy compared to methotrexate monotherapy in patients with active RA for 24 weeks.<sup>324</sup> Patients had previously not failed on methotrexate or biological agents. Patients (n=673) were randomized to tocilizumab 8 mg/kg IV every 4 weeks or methotrexate starting at 7.5 mg per week and titrated to 20 mg per week within 8 weeks or placebo for 8 weeks followed by tocilizumab 8 mg/kg. ACR 20 response rate was the primary endpoint; ACR 20 response rate was higher in the tocilizumab group compared to methotrexate (69.9% versus 52.5%;  $p<0.001$ ). The DAS28 rate of less than 2.6 was better with tocilizumab (33.6% versus 12.1%). Serious adverse events were reported in 3.8% of patients receiving tocilizumab and 2.8% of patients receiving methotrexate ( $p=0.5$ ). Serious infections were reported in 1.4% and 0.7% of patients receiving tocilizumab and methotrexate, respectively. Neutropenia (3.1% versus 0.4%) and elevated total cholesterol ( $\geq 240$  mg/dL; 13.2% versus 0.4%) were reported more frequently with tocilizumab than methotrexate, respectively.

In a double-blind, randomized, placebo-controlled study, the efficacy in achieving ACR 20 response with tocilizumab 623 patients with moderate to severe RA was evaluated over 24 weeks in the OPTION study.<sup>325</sup> Patients were randomized to IV tocilizumab 8 mg/kg (n=205), tocilizumab 4 mg/kg (n=214), or placebo every 4 weeks. Patients remained on the stable pre-study dose of methotrexate of 10 to 25 mg/week. At 24 weeks, ACR 20 response rates were 59% in the high-dose group, 48% in the low-dose group, and 26% in the placebo group (OR, 4; 95% CI, 2.6 to 6.1;  $p<0.0001$  for 8 mg/kg versus placebo; OR, 2.6; 95% CI, 1.7 to 3.9;  $p<0.0001$  for 4 mg/kg versus placebo). Serious infections or infestations were reported in 6 patients in the 8 mg/kg group, 3 patients in the 4 mg/kg group, and 2 patients in the placebo group.

In the double-blind, multicenter, randomized, controlled SATORI study, the efficacy and safety of tocilizumab monotherapy in 125 patients with active RA with an inadequate response to low-dose methotrexate were evaluated over 24 weeks.<sup>326</sup> Patients were randomized to IV tocilizumab 8 mg/kg every 4 weeks plus placebo or placebo plus methotrexate 8 mg/week for 24 weeks. The primary outcome measure was the ACR 20 response and the Disease Activity Score in 28 joints. After 24 weeks, 25% of the placebo plus methotrexate group and 80.3% in the tocilizumab group achieved ACR 20 response. The tocilizumab group showed superior ACR response criteria over control at all time points. Serious adverse events were reported in 4.7% and 6.6% of the methotrexate group and tocilizumab groups, respectively. Serious infections were reported in 1.6% and 3.3% of the methotrexate group and tocilizumab groups, respectively.

In a phase 3, double-blind, randomized, multicenter study, tocilizumab was compared to placebo in 499 patients with RA who had inadequate response to 1 or more TNF antagonists.<sup>327</sup> Patients were randomized to IV tocilizumab 8 mg/kg or 4 mg/kg or placebo given IV every 4 weeks with stable methotrexate for 24 weeks. ACR 20 response was achieved by 50%, 30.4%, and 10.1% of patients receiving tocilizumab 8 mg/kg, 4 mg/kg, or placebo, respectively (less than  $p<0.001$  both tocilizumab groups versus placebo). At week 4, more patients in the high-dose tocilizumab group achieved ACR 20

compared to the placebo group ( $p<0.001$ ). Patients responded regardless of the most recently failed anti-TNF treatment or the number of failed treatments. DAS28 remission rates at week 24 were dose-related with 30.1% ( $p<0.001$ ), 7.6% ( $p=0.053$ ), and 1.6% of the tocilizumab 8 mg/kg, 4 mg/kg, or placebo groups, respectively. The incidence of serious adverse events was higher in the placebo group (11.3%) compared to the tocilizumab high-dose group (6.3%) and low-dose group (7.4%).

In TOWARD, the efficacy and safety of tocilizumab in combination with other DMARDs were investigated in 1,220 patients with active RA.<sup>328</sup> In the phase 3, double-blind, placebo-controlled, multicenter study, patients remained on stable doses of DMARDs and received IV tocilizumab 8 mg/kg or placebo (control group) every 4 weeks for 24 weeks. At week 24, the proportion of patients achieving an ACR 20 was significantly greater in the tocilizumab plus DMARD group (61%) than in the control group (25%;  $p<0.0001$ ). Tocilizumab also provided greater improvement in the secondary endpoints including ACR 50 or ACR 70 responses, the DAS28, and DAS28 remission responses (DAS28<2.6). More adverse effects were reported in the tocilizumab group. Serious adverse effects were reported in 6.7% and 4.3% of patients in the tocilizumab and placebo groups, respectively. Elevated liver enzymes were observed in 4% and 1% of the tocilizumab and placebo groups, respectively. Elevated total cholesterol levels were reported in 23% and 6% of the tocilizumab and placebo groups, respectively.

The ROSE trial evaluated efficacy of tocilizumab in patients with moderate to severe active RA and inadequate clinical response to DMARDs.<sup>329</sup> Safety-related outcomes were also analyzed. In a 24-week, double-blind trial, patients with moderate to severe active RA and inadequate clinical response to DMARD therapy were randomized 2:1 to IV tocilizumab 8 mg/kg ( $n=412$ ) or placebo ( $n=207$ ) every 4 weeks while continuing background DMARD in both groups. The primary endpoint of ACR 50 response at week 24, was higher with tocilizumab versus placebo (30.1% versus 11.2%;  $p<0.0001$ ). Percentages of ACR 20 and ACR 50 responders were significantly higher with tocilizumab versus placebo as early as week-4 and continued to week 24; more patients in the tocilizumab arm also achieved ACR 70 responses beginning at week-8 compared to the placebo group ( $p<0.01$ ). A substudy examining early response to therapy showed improved patient global assessment of disease activity ( $p=0.005$ ) and pain ( $p=0.01$ ) and DAS28 ( $p=0.007$ ) with tocilizumab versus placebo at day-7. Safety findings were consistent with the known tocilizumab safety profile; rates of serious infections (per 100 patient-years) were 7.87 (95% CI, 4.3 to 13.2) and 1.2 (95% CI, 0.03 to 6.66) in the tocilizumab and placebo groups, respectively.

ADACTA was a randomized, double-blind, multicenter controlled phase 4 trial that compared IV tocilizumab monotherapy versus SC adalimumab monotherapy for adults with rheumatoid arthritis (diagnosed for at least 6 months) who were intolerant to methotrexate or for whom continuation of methotrexate was deemed inappropriate.<sup>330</sup> The study enrolled 326 patients who were randomized 1:1 (163 assigned to tocilizumab and 162 assigned to adalimumab). Patients previously treated with a biologic DMARD were excluded. Patients received either tocilizumab 8 mg/kg IV every 4 weeks plus placebo SC every 2 weeks or adalimumab 40 mg SC every 2 weeks plus placebo IV every four weeks for 24 weeks. The primary efficacy endpoint was change in disease activity score using 28 joints (DAS28; using erythrocyte sedimentation rate) from baseline to week 24. Key secondary efficacy endpoints were proportion of patients achieving a DAS28 of 3.2 or lower, a DAS28 of less than 2.6, ACR 20, 50, 70 responses, European League Against Rheumatism (EULAR) good response at week 24, and EULAR good or moderate response at week 24. A total of 24 of 163 (15%) of patients in the tocilizumab group and 28 of 163 (17%) of patients in the adalimumab group withdrew early from the study. Safety reasons for

withdrawal included adverse events (9 with tocilizumab and 10 with adalimumab) and death (2 for tocilizumab: 1 death was deemed unrelated to tocilizumab and 1 death was ruled possibly related to tocilizumab although the cause of death was not known and the patient had multiple cardiac comorbidities). Other reasons for withdrawal included insufficient treatment response (7 for tocilizumab, 14 for adalimumab), treatment refusal (3 for tocilizumab, 6 for adalimumab), and failure to return (3 for tocilizumab). The primary endpoint, mean change of DAS28 from baseline to week 24, was significantly greater with tocilizumab (-3.3) than with adalimumab (-1.8; difference -1.5; 95% CI, -1.8 to -1.1;  $p < 0.001$ ). Secondary endpoints at week 24 demonstrated significantly more patients in the tocilizumab group than in the adalimumab group had a DAS28 of 3.2 or less ( $p < 0.001$ ), a DAS28 of less than 2.6 ( $p < 0.001$ ), and ACR 20 ( $p = 0.0038$ ), 50 ( $p = 0.002$ ), 70 ( $p = 0.0023$ ) responses. EULAR responses were also more common in the tocilizumab group compared with the adalimumab group (EULAR good  $p < 0.001$ ; EULAR good or moderate  $p < 0.001$ ). The rates of adverse events were similar in each group, 82.1% for tocilizumab versus 82.7% for adalimumab. The most commonly reported adverse events were upper respiratory tract infections (11.1% for tocilizumab and 10.5% for adalimumab), nasopharyngitis (10.5% for tocilizumab versus 8% for adalimumab), and worsening of rheumatoid arthritis symptoms (6.8% for tocilizumab versus 9.9% with adalimumab). Incidence of serious adverse events was also similar between the groups; serious infections were the most common and were reported at similar proportions in both groups (23 in the tocilizumab group and 21 in the adalimumab group) with no specific type of infection predominating. More patients treated with tocilizumab than adalimumab needed dose modification or interruption because of adverse events, these were most commonly related to infections or laboratory abnormalities. The study sponsor, Hoffman-LA Roche, parent company of Genentech, designed the study, collected, analyzed, and interpreted the data, as well as wrote the report; the lead authors had full access to all the data.

### ***tocilizumab (Actemra) subcutaneous***

SUMMACTA: Study SC-1 was a randomized, double-blind, active-controlled, multicenter, non-inferiority study comparing tocilizumab 162 mg SC administered every week to tocilizumab 8 mg/kg IV every 4 weeks in patients  $> 18$  years of age with moderate to severe active RA.<sup>331,332</sup> A total of 1,262 patients with moderate to severe active RA diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline were randomized 1:1 to receive tocilizumab SC or IV in combination with non-biologic DMARD(s). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24. The pre-specified non-inferiority margin was a treatment difference of 12% or less. At week 24, 69% of the per protocol population who received tocilizumab SC had an ACR 20 compared to 73.4% of the patients who received tocilizumab IV. The weighted difference was -4% (95% CI, -9.2 to 1.2), demonstrating non-inferiority of tocilizumab SC administration to IV administration. Results of the SUMMACTA study at week 97 indicate that SC and IV tocilizumab have comparable long-term efficacy and safety, with the exception of injection site reactions being more common with the SC formulation.<sup>333</sup>

MUSASHI: This was a double-blind, double-dummy, parallel-group, comparative study of tocilizumab SC 162 mg every 2 weeks to tocilizumab IV 8 mg/kg every 4 weeks in Japanese patients.<sup>334</sup> Patients were 20 to 75 years of age and had RA for  $\geq 6$  months, diagnosed 1987 ACR criteria. Inclusion criteria included: an inadequate response of  $\geq 12$  weeks to any synthetic DMARD (methotrexate, salazosulfapyridine, bucillamine and leflunomide), biologic DMARD (infliximab, etanercept and adalimumab) or immunosuppressant (e.g., tacrolimus);  $\geq 8$  tender joints;  $\geq 6$  swollen joints; and an erythrocyte sedimentation rate (ESR) of  $\geq 30$  mm/hour or a C-reactive protein level of  $\geq 1$  mg/dL.

Patients (n=346) were randomized 1:1 into each treatment group and received drugs. No DMARDs or immunosuppressants were allowed during the study, although low dose corticosteroids and an NSAID were permitted. The primary endpoint was the ACR 20 response rate at week 24, with a prespecified tocilizumab SC to tocilizumab IV noninferiority margin of 18%. At week 24, the per protocol ACR 20 response was achieved in 79.2% (95% CI, 72.9 to 85.5) of the tocilizumab SC group and in 88.5% (95% CI, 83.4 to 93.5) of the tocilizumab IV group; and the weighted difference was -9.4% (95% CI, -17.6 to -1.2).

Study (SC-II) was a randomized, double-blind, placebo controlled, multicenter study in patients with active RA comparing tocilizumab 162 mg SC administered every other week to placebo.<sup>335</sup> Subjects were > 18 years of age with moderate to severe active RA, diagnosed according to ACR criteria, who had at least 8 tender joints and 6 swollen joints at baseline, and an inadequate response to their existing DMARD therapy. Patients (n=656) were randomized 2:1 to tocilizumab 162 mg SC every other week or placebo, in combination with non-biologic DMARD(s). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24. In SC-II, 61% of patients treated with tocilizumab 162 mg SC every other week achieved an ACR 20 response compared to 32% of placebo-treated patients in the intent to treat population with a weighted difference of 30% (95% CI, 22 to 37).

### **tofacitinib (Xeljanz, Xeljanz XR)**

Solo Study: A 6-month, randomized, double-blind, monotherapy study in 610 patients with moderate to severe active RA who had an inadequate response to a DMARD (non-biologic or biologic).<sup>336</sup> Patients were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo. At the Month 3 visit, all patients on placebo were switched to tofacitinib 5 or 10 mg twice daily. Primary efficacy endpoints were ACR 20, Health Assessment Questionnaire-Disability Index (HAQ-DI), and DAS28 < 2.6 at Month 3. A greater proportion of patients on tofacitinib 5mg or 10 mg had ACR 20 responses compared to placebo (59.8% and 65.7% versus 26.7%, respectively;  $p \leq 0.05$  for both). ACR 50 and ACR 70 responses were consistent with the ACR 20 results. ACR 20, ACR 50, and ACR 70 responses were numerically higher for tofacitinib 10 mg compared 5 mg at all time points; the differences between the dosages were most pronounced for ACR 70. The differences in HAQ-DI from placebo were similar between the 5 mg and 10 mg dose groups (0.5 and 0.57, versus 0.19, respectively;  $p < 0.0001$  for both). ACR 20 and HAQ-DI efficacy responses were observed starting at Week 2 and were maintained throughout the study. The proportion of patients achieving DAS28-4(ESR) < 2.6 at Month 3 was numerically but not statistically significantly greater for both tofacitinib dosages (5.6% and 8.7% versus 4.4%, respectively).

Scan, Sync, and Standard Studies: Three 12-month double-blind phase 3 studies included patients with moderate to severe active RA who had an inadequate response to a non-biologic DMARD, including methotrexate.<sup>337</sup> In the Scan study, patients (n=797) received tofacitinib 5 or 10 mg twice daily or placebo added to background methotrexate treatment; Sync study patients (n=792) received tofacitinib 5 or 10 mg twice daily or placebo added to background DMARDs; Standard study patients (n=717) received tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background methotrexate. The co-primary endpoints for all 3 studies were the proportion of patients who achieved an ACR 20 response at Month 6, changes in HAQ-DI at Month 3, and rates of DAS28-4(ESR) < 2.6 at Month 6. In the studies 45 to 49% of placebo patients were considered nonresponders (e.g., those not reaching ACR 20) and were switched to tofacitinib 5 mg or 10 mg twice daily at Month 3. At the end of Month 6, all placebo patients were switched to tofacitinib 5 mg or 10 mg twice daily. ACR 20 response rate was greater in patients treated with tofacitinib 5 mg

or 10 mg compared with placebo (47.3% to 61.8% and 51.5% to 52.7% versus 25.3% to 31.2%, respectively). Placebo patients rapidly responded after advancing to tofacitinib. The proportion of patients who achieved ACR 20 response was similar in the tofacitinib treatment groups and the adalimumab treatment group (51.5% and 52.6%, versus 47.3%, respectively). ACR 50 response rates were greater in the tofacitinib 5 mg treatment group than in the adalimumab treatment group at Month 3 ( $p \leq 0.05$ ); although at Month 6 neither dose of tofacitinib was statistically significantly different to adalimumab. ACR 70 response rates were better in both tofacitinib dose groups than in the adalimumab group at Month 6 ( $p \leq 0.0019$ ). The changes from baseline in HAQ-DI were similar or better for tofacitinib 5 mg or 10 mg than that seen for adalimumab group during the entire treatment period (0.56 and 0.64 versus 0.51, respectively). The proportion of patients achieving DAS28-4(ESR)  $< 2.6$  at the primary time point was statistically significantly different from the placebo group for both tofacitinib dose groups across the phase 3 background DMARD studies ( $p < 0.05$ ). The proportions for the tofacitinib 10 mg dose group were notably greater than for the 5 mg dose group.

The Scan study also assessed progression of structural damage using modified Total Sharp Score (mTSS) at Month 6; no progression in mTSS was defined as  $\leq 0.5$  unit increase from baseline. At baseline treatment groups were similar in degree of damage as shown on x-ray and their estimated annual rate of progression. Changes in mean mTSS at Month 6 for tofacitinib 5mg and 10 mg and placebo were 0.12, 0.06, and 0.47, respectively; this represented approximately 74% and 87% reductions relative to placebo, respectively. The difference compared to placebo was statistically significant for the 10 mg dose ( $p = 0.0376$ ) at Month 6; but not for the 5 mg dose ( $p = 0.0792$ ). Reductions continued through Month 12. The proportion of patients with no progression of mTSS for both tofacitinib doses (88.8% for 5 mg, 86.9% for 10 mg) was statistically greater than placebo (77.7%) at Month 6. Effect of tofacitinib on inhibition of the progression of structural damage was maintained for up to 12 months.

**Step Study:** The Step Study was a 6-month phase 3 trial in 399 patients with moderate to severe active RA who had an inadequate response to at least 1 TNF-inhibitor biologic agent.<sup>338</sup> These patients received tofacitinib 5 mg or 10 mg twice daily or placebo added to background methotrexate treatment. At Month 3, all patients on placebo treatment were switched to tofacitinib 5 mg or 10 mg twice daily. The primary endpoints were the proportion of patients who achieved an ACR 20 response, HAQ-DI, and DAS28-4(ESR)  $< 2.6$  at Month-3. ACR 20 response rate for tofacitinib 5 mg and 10 mg and placebo were 41.7, 48.01, and 24.4%, respectively. Changes from baseline in HAQ-DI were 0.43, 0.46, and 0.18, respectively. Proportion of patients with DAS28  $< 2.6$  were 8.8%, 6.7%, and 1.7%, respectively. The authors noted that the magnitudes of these improvements tended to be lower in this trial than in the other background DMARD studies, which was expected for patients with biologic DMARD refractory RA.

Approval of extended-release tofacitinib (Xeljanz XR) was based on efficacy and safety data established with immediate-release tofacitinib.

## Ulcerative Colitis

### *adalimumab (Humira)*

Study UC-I, was a randomized, double-blind, placebo-controlled study in 390 TNF-blocker naive adults with moderate to severe active UC (Mayo score 6 to 12 on a 12-point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants

including corticosteroids, azathioprine, or 6-mercaptopurine (6-MP).<sup>339</sup> Patients were randomized to 1 of 3 treatment groups, which included placebo or 1 of 2 different regimens of adalimumab. Concomitant stable doses of aminosaliclates and immunosuppressants, including corticosteroids, azathioprine, and 6-MP were permitted. The placebo group received doses at weeks 0, 2, 4, and 6. The first treatment group, (160/80), received adalimumab 160 mg at week 0 and 80 mg at week 2, and the second treatment group, (80/40), received adalimumab 80 mg at week 0 and 40 mg at week 2. After week 2, patients in both treatment groups received 40 mg every other week. Induction of clinical remission was defined as a Mayo score  $\leq 2$  with no individual subscores  $> 1$  at week 8. A total of 18.5% of subjects receiving adalimumab 160/80 mg achieved a clinical remission at 8 weeks compared to 9.2% of subjects receiving placebo (treatment difference, 9.3%; 95% CI, 0.9 to 17.6;  $p < 0.05$  using a pairwise comparison of proportions). In the adalimumab 80/40 mg group and the placebo group at week 8, there was no statistically significant difference in clinical remission. Study UC-II, was a randomized, double-blind, placebo-controlled study in 518 TNF-blocker naive adult patients with moderate to severe active UC (Mayo score 6 to 12 on a 12 point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP or who had lost response or were intolerant to TNF blockers.<sup>340</sup> Forty percent of patients had previously used another TNF blocker. Patients were randomized to either placebo or adalimumab. Concomitant stable doses of aminosaliclates and immunosuppressants, including corticosteroids, azathioprine, and 6-MP were permitted. Subjects received either placebo at weeks 0, 2, 4, and 6 or an initial dose of adalimumab 160 mg at week 0 and 80 mg at week 2. After week 2, patients received 40 mg every other week. Induction of clinical remission was defined as a Mayo score  $\leq 2$  with no individual subscores  $> 1$  at week 8. Clinical remission at week 52 and sustained clinical remission (defined as clinical remission at both weeks 8 and 52) were evaluated. A total of 16.5% of subjects receiving adalimumab 160/80 mg achieved a clinical remission at 8 weeks compared to 9.3% of subject receiving placebo (treatment difference, 7.2%; 95% CI, 1.2 to 12.9). The rate of sustained clinical remission was 8.5% for adalimumab 160/80 mg and 4.1% for placebo for a treatment difference of 4.4% (95% CI, 0.1 to 8.6). Both the rate of induction of clinical remission at 8 weeks and the rate of sustained clinical remission for adalimumab 160/80 mg were statistically significant ( $p < 0.05$  using a pairwise comparison of proportions). Rates of clinical remission at week 52, were 17.3% for adalimumab compared to 8.5% for placebo (treatment difference, 8.8%; 95% CI, 2.8 to 14.5;  $p < 0.05$ ). The safety profile with adalimumab in patients with ulcerative colitis was reported as similar to the profile seen in patients with rheumatoid arthritis.

### ***golimumab (Simponi)***

The phase 3 portion of the PURSUIT-SC trial was a randomized, double-blind, placebo-controlled, 6-week induction trial in 771 patients  $\geq 18$  years of age with moderately to severely active ulcerative colitis (Mayo score 6 to 12).<sup>341</sup> Subjects also had an endoscopy subscore of 2 or 3 on a 3-point scale, and were corticosteroid dependent, or had an inadequate response or failed to tolerate at least 1 of the following: aminosaliclates, oral corticosteroids, azathioprine, or 6-mercaptopurine (6-MP). Subjects were randomized to the following subcutaneous treatments at week 0 and week 2: placebo at both weeks, 200 mg followed by 100 mg, or 400 mg followed by 200 mg. The primary endpoint was the percent of responders at week 6, defined as a decrease from baseline in the Mayo score by  $\geq 30\%$  and  $\geq 3$  points, accompanied by a decrease in the rectal bleeding subscore of  $\geq 1$  or a rectal bleeding subscore of 0 (no blood seen) or 1 (streaks of blood with stool less than half the time). Stable doses of oral aminosaliclates, oral corticosteroids (less than 40 mg/day), azathioprine, 6-MP, and/or

methotrexate were permitted. Patients who received TNF inhibitors previously were excluded. Fifty-two percent of patients receiving golimumab 200 mg/100 mg had a response at week 6 compared to 30% of patients on placebo for a treatment difference of 22% (95% CI, 14 to 30%;  $p<0.0001$ ). There was no additional benefit in the 400 mg/200 mg group and the 100 mg 50 mg group did not show a response.

PURSUIT-M was a randomized, double-blind, placebo-controlled, 54-week maintenance trial in 463 patients  $\geq 18$  years of age with moderate to severely active ulcerative colitis who achieved a clinical response with golimumab induction at 6 weeks and who tolerated therapy.<sup>342</sup> Subjects were randomized to placebo, golimumab 50 mg or 100 mg subcutaneously every 4 weeks. Concomitant oral aminosalicylates, azathioprine, 6-MP, and/or methotrexate were permitted if doses were stable. Corticosteroid dosage was tapered at the start of treatment. The clinical response was assessed every 4 weeks and the primary endpoint was the percent of patients maintaining a clinical response through week 54. Fifty-one percent of patients receiving golimumab 100 mg ( $n=154$ ) maintained a clinical response through week 54 as compared to 31% of placebo patients ( $n=156$ ) for a treatment difference of 19% (95% CI, 8 to 30;  $p<0.001$ ).

### ***infliximab (Remicade)***

The efficacy of infliximab for induction and maintenance therapy in adults with moderate to severe active ulcerative colitis was evaluated in 2 randomized, double-blind, placebo-controlled studies (ACT1 and ACT2).<sup>343</sup> Each study had 364 patients who received either placebo or infliximab 5 or 10 mg/kg of body weight IV at weeks 0, 2, and 6 and then every 8 weeks through week 46 (ACT1) or week 22 (ACT2). Patients were followed for 54 weeks in ACT1 and 30 weeks in ACT2. By week 8 in ACT1, clinical response (defined as a decrease in Mayo score of at least 3 points and decrease of 30% with a decrease in rectal bleeding measured by 2 scales) was seen in 69%, 61%, and 37% of patients receiving infliximab 5 mg, infliximab 10 mg, and placebo, respectively ( $p<0.001$  for both comparisons to placebo). In ACT2, the clinical response rates were 64%, 69%, and 29% ( $p<0.001$  for both comparisons to placebo). At week 30, patients receiving infliximab were more likely to have a clinical response ( $p\leq 0.002$  for all comparisons). At week 52 in ACT1, the clinical response rates were 45% and 44% for infliximab 5 and 10 mg, respectively, compared to 20% in the placebo group ( $p<0.001$  for both comparisons).

### ***vedolizumab (Entyvio)***

Two randomized, double-blind, placebo-controlled trials (UC Trials I and II) were conducted to evaluate the safety and efficacy of vedolizumab in adult patients with moderately to severely active UC.<sup>344</sup> Severely active UC was defined in both trials as a Mayo score of 6 to 12 with endoscopy subscore of 2 or 3. Enrolled patients in the U.S. had over the previous 5-year period an inadequate response or intolerance to immunomodulator therapy (e.g., thiopurines [azathioprine or mercaptopurine]) and/or an inadequate response, loss of response, or intolerance to a TNF blocker. Outside the U.S., prior treatment with corticosteroids was sufficient for entry if over the previous 5-year period the patients were corticosteroid dependent or had an inadequate response or intolerance to corticosteroids. Patients that had ever received natalizumab and patients that had received a TNF blocker in the past 60 days were excluded from enrollment.

In UC Trial I, patients ( $n=374$ ) were randomized in a double-blind fashion (3:2) to receive vedolizumab 300 mg or placebo by intravenous (IV) infusion at Week 0 and Week 2. Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were permitted through Week 6 and efficacy assessments were conducted at Week 6. A total of 39% of patients had an inadequate

response, loss of response, or intolerance to TNF blocker therapy and 18% only had an inadequate response, inability to taper or intolerance to prior corticosteroid treatment. The median baseline Mayo score was 9 in the vedolizumab group and 8 in the placebo group. In UC Trial I, a greater percentage of patients treated with vedolizumab compared to patients treated with placebo (47% versus 26%,  $p < 0.001$ ) achieved clinical response at Week 6. A greater percentage of patients treated with vedolizumab compared to patients treated with placebo (17% versus 5%,  $p = 0.001$ ) also achieved clinical remission and improvement of endoscopic appearance of the mucosa (25% versus 41%,  $p = 0.001$ ) at Week 6.

In UC Trial II, 373 patients who had a clinical response to vedolizumab at Week 6 were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: vedolizumab 300 mg every 8 weeks, vedolizumab 300 mg every 4 weeks, or placebo every 4 weeks. Concomitant aminosalicylates and corticosteroids were permitted through Week 52 and efficacy assessments occurred at week 52. Concomitant immunomodulators were permitted outside the U.S. but were not permitted beyond Week 6 in the U.S. At Week 6, patients were receiving corticosteroids (61%), immunomodulators (32%) and aminosalicylates (75%). A total of 32% of patients had an inadequate response, loss of response or intolerance to a TNF blocker therapy. At Week 6, the median Mayo score was 8 in all 3 groups. Patients who had achieved clinical response at Week 6 and were receiving corticosteroids were required to begin a corticosteroid tapering regimen at Week 6. In the trial, a greater percentage of patients in groups treated with vedolizumab as compared to placebo (42% versus 16%,  $p < 0.001$ ) achieved clinical remission at Week 52 and maintained clinical response (57% versus 24 %,  $p < 0.001$ ). In addition, a greater percentage of patients in groups treated with vedolizumab as compared to placebo were in clinical remission at both Weeks 6 and 52 (21% versus 9%,  $p < 0.001$ ), and had improvement of endoscopic appearance of the mucosa at Week 52 (52% versus 20%,  $p < 0.001$ ). The vedolizumab every 4-week dosing regimen did not demonstrate additional clinical benefit over the every 8-week dosing regimen and is not the recommended dosing regimen.

## **Uveitis**

### **adalimumab (Humira)**

The efficacy of adalimumab for the treatment of non-infectious intermediate, posterior, and panuveitis was established in 2 double-masked, placebo-controlled, randomized clinical trials (VISUAL I,  $n = 217$ ; VISUAL II,  $n = 226$ ). In each trial, patients were randomized 1:1 to either placebo or adalimumab SC 80 mg for 1 dose then 40 mg every other week beginning 1 week following the initial dose. VISUAL I included patients with active uveitis treated with oral prednisone 10 to 60 mg/day and underwent a steroid tapering schedule (discontinued by week 15).<sup>345,346</sup> VISUAL II included patients with inactive uveitis treated with oral corticosteroids 10 to 35 mg/day who also underwent a steroid tapering schedule (discontinued by week 19). Patients with anterior uveitis were excluded in both trials. In both studies, the primary endpoint was time to treatment failure, defined as the development of inflammatory chorioretinal and/or vascular lesions, increased anterior chamber (AC) cell grade or vitreous haze (VH) grade, or a decrease in best corrected visual acuity (BCVA). In VISUAL I, treatment with adalimumab resulted in a lower percentage of patient treatment failures (78.5% versus 54.5% for placebo and adalimumab, respectively; HR, 0.5; 95% CI, 0.36 to 0.7). The median time to failure was 3 months (95% CI, 2.7 to 3.7) with placebo compared to 5.6 months (95% CI, 3.9 to 9.2) with adalimumab. In VISUAL II, treatment with adalimumab also resulted in a lower percentage of patient treatment failures (55% versus 39.1% for placebo and adalimumab, respectively; HR, 0.57; 95% CI, 0.39

to 0.84). The median time to failure was 8.3 months (95% CI, 4.8 to 12) with placebo and was not estimable (> 18 months) with adalimumab due to limited failure events.

## META-ANALYSES

### Ankylosing Spondylitis

A meta-analysis of 18 randomized controlled trials involving anti-TNF agents (4 adalimumab versus placebo, 8 etanercept versus placebo, 2 golimumab versus placebo, 3 infliximab versus placebo, and 1 etanercept versus infliximab) for the treatment of ankylosing spondylitis.<sup>347</sup> Most included trials allowed for the use of concomitant stable traditional DMARDs, NSAIDs, or corticosteroids. The anti-TNF agents were more likely than placebo to achieve an ASAS 40 response before 6 months (adalimumab: risk ratio [RR], 3.53 [95% credible interval (CrI), 2.49 to 4.91]; etanercept: RR 3.31 [95% CrI, 2.38 to 4.53]; golimumab: RR 2.9 [95% CrI, 1.9 to 4.23]; and infliximab: RR 4.07 [95% CrI, 2.8 to 5.74]). The number needed to treat (NNT) ranged from 3 to 11 to achieve an ASAS partial. Withdrawals due to adverse events in the anti-TNF group were higher than with placebo, but the absolute increase in harm was small. Trials were of a short duration (24 weeks or less) and most were funded by the manufacturer of the product.

A second meta-analysis on the use of anti-TNF agents also included patients with axial spondyloarthritis (20 double-blind, randomized controlled trials: 15 AS, 4 axial spondyloarthritis, and 1 with both).<sup>348</sup> In AS patients, anti-TNF agents showed better efficacy than placebo for BASDAI (effect size, 1; 95% CI, 0.87 to 1.13), BASFI (effect size, 0.67; 95% CI, 0.58 to 0.76) and ASAS 40 response (odds ratio [OR], 4.7; 95% CI, 3.8 to 6).

A more recent network meta-analysis of 14 randomized controlled trials (n=2,672) compared the efficacy of biologic regimens in the treatment of AS based on week 12 or 14 ASAS20 improvement.<sup>349</sup> Most trials were compared to placebo, and the meta-analysis included non-U.S. clinical trials. Biologics included in the meta-analysis were adalimumab, etanercept, infliximab, golimumab, secukinumab, and tocilizumab. The authors found no overall differences in efficacy for AS, but noted infliximab was superior to tocilizumab (OR, 4.81; 95% CrI, 1.43 to 17.4), although tocilizumab is not indicated for AS. However, the relatively small number and size of studies may limit these results.

### Crohn's Disease

A systematic review evaluated infliximab (Remicade), adalimumab (Humira), and certolizumab (Cimzia) in the maintenance of remission in Crohn's disease.<sup>350</sup> Literature from 1966 to 2007 was reviewed and nine studies met inclusion criteria. Studies considered included randomized controlled trials involving patients > 18 years with Crohn's disease who had a clinical response or clinical remission with a TNF-blocking agent, or patients with Crohn's disease in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-blocking agent or placebo. Infliximab maintains clinical remission, maintains clinical response, has corticosteroid-sparing effects, and maintains fistula healing in patients with Crohn's disease having a response to infliximab induction therapy. There were no significant differences in remission rates between infliximab doses of 5 mg/kg or 10 mg/kg. Adalimumab maintains clinical remission, maintains clinical response, and has corticosteroid-sparing effects in patients with Crohn's disease who have responded or entered remission with adalimumab induction therapy. There were no significant differences in remission rates between adalimumab 40 mg weekly or every other week. There is evidence from one randomized

controlled trial that certolizumab maintains clinical remission and maintains clinical response in patients who have responded to certolizumab induction therapy.

A systematic review found that infliximab, based on literature available through 2005, was effective in inducing clinical remission and response in patients with moderate to severe ulcerative colitis with refractory disease.<sup>351</sup> The need for colectomy was reduced in short-term trials with infliximab.

Another meta-analysis included 14 trials with 3,995 patients with Crohn's disease who were treated with infliximab, adalimumab, or certolizumab.<sup>352</sup> The primary endpoints were clinical remission for luminal Crohn's disease and fistula closure at  $\geq 2$  consecutive visits. In overall analysis, TNF blockers were effective for induction of remission at week 4 (mean difference, 11%; 95% CI, 6 to 16;  $p < 0.001$ ) and maintenance of remission at weeks 20 to 30 in patients who responded to induction therapy and in patients randomized before induction (mean difference, 23%; 95% CI, 18 to 28; and mean difference, 8%; 95% CI, 3 to 12%, respectively;  $p < 0.001$  for all comparisons). In the 10 studies evaluating TNF blockers for fistulizing Crohn's disease ( $n = 776$  patients), TNF blockers were effective for fistula closure only in maintenance trials following open-label induction (mean difference, 16%; 95% CI, 8 to 25%;  $p < 0.001$ ). In the 21 studies evaluated for safety, TNF blockers did not increase the risk of death, malignancy, or serious infection.

## Psoriasis

A systematic review evaluated the efficacy and safety of biologic agents in the treatment of plaque psoriasis.<sup>353</sup> Randomized, controlled, double-blind, monotherapy trials of alefacept ( $n = 3$ ), efalizumab ( $n = 5$ ), etanercept ( $n = 4$ ) and infliximab ( $n = 4$ ) with a total of 7,931 patients met inclusion criteria. Efficacy was measured by PASI 75 achievement after 10 to 14 weeks of treatment, using intention-to-treat analysis. All biological agents for psoriasis were efficacious ( $p < 0.001$ ); however, there was a graded response for achievement of PASI 75: infliximab (pooled relative risk [RR], 17.4; NNT=2), etanercept (RR, 11.73; NNT=3), and alefacept (RR, 0.7; NNT=8). The risk of 1 or more adverse events was evaluated by RR and number needed to harm (NNH). This was increased in the alefacept (RR, 1.09;  $p = 0.03$ ; NNH=15) and infliximab (RR, 1.18;  $p < 0.001$ ; NNH=9) groups compared with placebo.

Another systematic review evaluated 24 clinical trials with 9,384 patients with moderate to severe psoriasis.<sup>354</sup> Sixteen double-blind trials were included. Based on PASI 75 at weeks 8 to 16 in the trials, infliximab was significantly superior to all other interventions (risk difference [RD], 77%; 95% CI, 72 to 81). Adalimumab (RD, 64%; 95% CI, 61 to 68) was superior to cyclosporine (RD, 33%; 95% CI, 13 to 52), etanercept 50 mg twice weekly (RD, 44%; 95% CI, 40 to 48) and etanercept 25 mg twice weekly (RD, 30%; 95% CI, 25 to 35).

A systematic literature review and meta-analysis compared the efficacy of psoriasis treatments.<sup>355</sup> Randomized controlled trials evaluating PASI were identified and evaluated for quality. PASI responses were modeled using a mixed-treatment comparison, which enabled the estimation of the relative effectiveness of several treatments. A total of 22 trials were included. TNF inhibitors were most likely to achieve PASI 75, with a mean relative risk (RR) of 15.57 (95% CI, 12.46 to 19.25) versus mean RRs of 9.24 (95% CI, 5.33 to 13.91) for systemic and 5.65 (95% CI, 3.74 to 7.97) for T-cell therapies. Infliximab (81%) and adalimumab (71%) had greater probabilities of achieving PASI 75 than etanercept (50%), although dosage was an important determinant of outcome.

## Psoriatic Arthritis

A meta-analysis evaluated the efficacy and safety of TNF blockers in the management of PsA.<sup>356</sup> Six randomized controlled trials with 982 patients investigated adalimumab, etanercept, and infliximab. All 3 TNF blockers were significantly more effective than placebo on Psoriatic Arthritis Response Criteria (PsARC) and ACR 20, ACR 50, and ACR 70 ratings. There were no significant differences between TNF-alpha inhibitors and placebo in the proportions of patients experiencing withdrawal for any reason (RR, 0.48; 95% CI, 0.2 to 1.18), or withdrawal due to adverse events (RR, 2.14; 95% CI, 0.73 to 6.27), serious adverse events (RR, 0.98; 95% CI, 0.55 to 1.77), or upper respiratory tract infections (RR, 0.91; 95% CI, 0.65 to 1.28). Pooled injection site reactions were significantly higher for adalimumab and etanercept than for placebo (RR, 2.48; 95% CI, 1.16 to 5.29), but there was no significant difference in the proportion of patients experiencing infusion reactions with infliximab (RR, 1.03; 95% CI, 0.48 to 2.2) compared against placebo.

## Rheumatoid Arthritis

A meta-analysis of 13 clinical trials with etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade), or anakinra (Kineret) were included in a systematic review of the literature in the management of RA.<sup>357</sup> Efficacy was based on ACR 20 or ACR 50 response after 6 months of therapy. In all trials, active treatment was efficacious in comparison to placebo or methotrexate. For each treatment, the inclusion of methotrexate in combination improved the response. After adjustment for study-level variables, the authors found TNF $\alpha$  antagonists to be more efficacious compared with anakinra ( $p < 0.05$ ). Indirect comparisons between the 3 TNF $\alpha$  antagonists indicated no difference in efficacy. Author findings included treatment with anakinra is better than placebo; for each treatment, the use of combination methotrexate improves the probability of response; treatment with any of the TNF $\alpha$  antagonists is better than with anakinra; and all drugs in the TNF $\alpha$  antagonist class are no different from each other. Findings from another systematic review from 2006 were similar.<sup>358</sup>

A systematic review analyzed the efficacy and safety of anti-TNF drugs (infliximab, etanercept, and adalimumab) for treating RA.<sup>359</sup> A total of 13 articles with 7,087 patients met inclusion criteria. All studies were at least 6 months in duration and evaluated response to treatment using ACR 20, ACR 50, and ACR 70. The combined relative risk to achieve a therapeutic response to treatment with recommended doses of any TNF blocker was 1.81 (95% CI, 1.43 to 2.29) with a number-needed-to-treat (NNT) of 5 for ACR 20, 5 for ACR 50, and 7 for ACR 70. Overall therapeutic effects were also similar regardless of the specific TNF blocker used, as well as when higher-than-recommended doses were administered. However, lower-than-recommended doses elicited low ACR 70 responses (NNT=15). For patients with an insufficient prior response to methotrexate, the TNF blockers plus methotrexate had NNT values of 3 for ACR 20, 4 for ACR 50, and 8 for ACR 70. Comparisons of anti-TNF drugs plus methotrexate versus methotrexate alone in patients with no previous resistance to methotrexate showed somewhat lower effects. Adverse effects were more likely with TNF blockers than controls (overall combined NNH=27). Patients receiving infliximab were more likely to withdraw because of adverse effects (NNH=24) and to suffer severe adverse effects (NNH=31), infections (NNH=10), and infusion reactions (NNH=9). Patients receiving adalimumab were also more likely to drop out because of side effects (NNH=47) and to suffer injection site reactions (NNH=22). Patients receiving etanercept were less likely to drop out because of side effects (NNH for control versus etanercept, 26) but more likely to experience injection site reactions (NNH=5).

A meta-analysis compared the benefits and safety of abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab in patients with RA.<sup>360</sup> ACR 50 response rates were the major outcomes evaluated. A mixed-effects logistic regression was used to provide an indirect comparison of the treatment effects between the biologics. The biologics reported higher ACR 50 rates compared to placebo (OR, 3.35; 95% CI, 2.62 to 4.29) and a NNT for benefit of 4 (95% CI, 4 to 6). Discontinuations due to adverse events were higher with the biologics (OR, 1.39; 95% CI, 1.13 to 1.71), with a NNH of 52 (95% CI, 29 to 152). Anakinra was less effective than all of the other biologics, although this difference was statistically significant only for the comparison with adalimumab (OR, 0.45; 95% CI, 0.21 to 0.99) and etanercept (OR, 0.34; 95% CI, 0.14 to 0.81). Adalimumab, anakinra, and infliximab were more likely than etanercept to lead to withdrawals related to adverse events (adalimumab OR, 1.89 [95% CI, 1.18 to 3.04]; anakinra OR, 2.05 [95% CI, 1.27 to 3.29]; and infliximab OR 2.7 [95% CI, 1.43 to 5.26]).

A meta-analysis evaluated the efficacy and safety of using the TNF antagonists including adalimumab, etanercept, and infliximab in the treatment of adults with RA.<sup>361</sup> A total of 21 randomized, placebo-controlled trials were included. A total of 1,524 patients with adalimumab, 1,116 patients received infliximab, and 1,029 patients received etanercept, and 2,834 patients received placebo with or without methotrexate in all groups. Efficacy was compared using ACR 20, ACR 50, and ACR 70 criteria. In the short term trials (12 to 30 weeks), etanercept had the highest risk ratios for reaching ACR 20 and ACR 50: 2.94 (95% CI, 2.27 to 3.81) and 5.28 (95% CI, 3.12 to 8.92), respectively. ACR 70 achievement was highest with adalimumab (5.36; 95% CI, 3.76 to 7.64). Over long-term treatment (1 to 3 years), adalimumab demonstrated the highest risk ratios for ACR 20 (1.85; 95% CI, 1.07 to 3.19), ACR 50 (2.8; 95% CI, 1.16 to 6.77), and ACR 70 (3.23; 95% CI, 1.37 to 7.61). No significant differences were observed between the active treatments and placebo.

A systematic review of 16 randomized controlled trials comparing the efficacy of anti-TNF agents with placebo at 24 weeks in patients who have had an inadequate response to methotrexate was performed.<sup>362</sup> Relative efficacy was estimated using Bayesian mixed treatment comparison (MTC) models. Three different outcome measures were used: ACR 20 and ACR 50 response and the percentage improvement in Health Assessment Questionnaire (HAQ) score. All anti-TNF agents showed significantly improved efficacy over placebo. The results also provide evidence of some differences in efficacy among the agents. Etanercept was favored over infliximab and golimumab, and certolizumab was favored over infliximab and adalimumab. ACR results indicate improved efficacy of certolizumab over golimumab. On HAQ analysis, adalimumab, certolizumab, etanercept and golimumab appear superior to infliximab, and etanercept shows improved efficacy compared with adalimumab.

A total of 18 published trials and 1 abstract were included in a meta-analysis examining the efficacy of a biological agent in RA at 6 months in patients with an incomplete response to methotrexate or an anti-TNF biologic.<sup>363</sup> In patients with incomplete response to methotrexate, anti-TNF agents had the same probability of reaching an ACR 50 compared to non-anti-TNF biologicals taken together (OR, 1.3; 95 % CI, 0.91 to 1.86). However, when compared to specific biological agents, anti-TNFs demonstrated a higher probability of reaching an ACR 50 than abatacept (OR, 1.52; 95 % CI, 1 to 2.28), but not in comparison to rituximab and tocilizumab. In patients with prior incomplete response to anti-TNF agents, rituximab demonstrated a higher probability of achieving an ACR 50 than tocilizumab (OR, 2.61; 95% CI, 1.1 to 6.37), but no significant differences existed between golimumab and other biologicals.

A meta-analysis including similarly designed double-blind, randomized, placebo-controlled trials over an 18-year period compared the response of tocilizumab and other biologic agents in patients with RA who had inadequate response to DMARD therapy.<sup>364</sup> Biologic agents included abatacept, rituximab,

etanercept, infliximab, adalimumab, and tocilizumab. The endpoint of interest was ACR 20/50/70 response criteria at 24 to 30 weeks. The effectiveness of tocilizumab appeared to be comparable to that of other biologic agents for ACR 20 and ACR 50 responses but greater for ACR70. Specifically, tocilizumab had greater ACR70 responses than both TNF-alpha inhibitors (RR, 1.8; credible interval [CrI], 1.2 to 2.6) and abatacept (RR, 2; CrI, 1.3 to 3.1).

A network meta-analysis of 28 randomized controlled trials compared the efficacy of novel DMARDs (abatacept, anakinra, adalimumab, certolizumab, etanercept, golimumab, infliximab, tocilizumab, or tofacitinib) as monotherapy or with methotrexate on ACR response at 24 weeks.<sup>365</sup> Most novel DMARDs with methotrexate demonstrated comparable efficacy with the exception of anakinra with methotrexate. When compared as monotherapy, greater response was seen with tocilizumab compared to other anti-TNF agents or tofacitinib, and efficacy of tocilizumab with methotrexate was similar to tocilizumab monotherapy (OR, 1.08 [95% CrI, 0.4 to 2.84]; OR, 1.24 [95% CrI, 0.44 to 3.61]; and OR, 0.95 [95% CrI, 0.33 to 2.72] for ACR 20, ACR 50, and ACR 70, respectively; however, the efficacy of anti-TNF agents with methotrexate appears superior to the anti-TNF agents used as monotherapy (OR, 2.41 [95% CrI, 0.51 to 11.61]; OR, 2.85 [95% CrI, 0.51 to 17.67]; and OR, 1.28 [95% CrI, 0.21 to 8.42] for ACR 20, ACR 50, and ACR 70, respectively. Overall, the number of studies available for inclusion limited the results and, in most cases, the credible intervals were broad.

A Cochrane review assessed the benefits of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib in patients with RA who have failed to respond to methotrexate or DMARDs (79 randomized controlled trials; n=32,874).<sup>366</sup>

## Safety

A meta-analysis of 9 clinical trials (3 to 12 months duration involving nearly 3,500 patients) of adalimumab (Humira) and infliximab (Remicade) identified a dose-related increase in the incidence of malignancies (OR, 3.3; 95% CI, 1.2 to 9.1) compared with placebo.<sup>367</sup> Infections requiring antimicrobial therapy also occurred at a higher rate in the active treatment groups compared to placebo (OR, 2; 95% CI, 1.3 to 3.1).

A meta-analysis of nine trials of longer than 12 weeks durations involving 3,316 patients of which 2,244 received etanercept for the treatment of RA evaluated the risk of malignancies.<sup>368</sup> A total of 26 patients in the etanercept group (incidence rate 10.47/1,000 person-years) were diagnosed with a malignancy. In the control group, 7 patients had a diagnosis of malignancy (incidence rate of 6.66/1,000 person-years); the results were not statistically significant. A Cox's proportional hazards, fixed-effect model stratified by trial yielded a hazard ratio of 1.84 (95% CI, 0.79 to 4.28) for the etanercept group compared with the control group.

A systematic review of the TNF antagonists to evaluate the risk of infection and malignancy in patients with plaque psoriasis and psoriatic arthritis included randomized, placebo-controlled trials of etanercept, infliximab, adalimumab, golimumab, and certolizumab.<sup>369</sup> A total of 20 studies with 6,810 patients were included. The odds ratios for overall infection and serious infection over a mean of 17.8 weeks were 1.18 (95% CI, 1.05 to 1.33) and 0.7 (95% CI, 0.4 to 1.21), respectively. The odds ratio for malignancy was 1.48 (95% CI, 0.71 to 3.09) and 1.26 (95% CI, 0.39 to 4.15) when nonmelanoma skin cancer was excluded. In the short term, the authors concluded that there is a small risk of overall infection with the TNF antagonists. No evidence of an increased risk of serious infection or malignancy was observed in the short-term trials.

## SUMMARY

Cytokines and CAMs have been implicated in RA, plaque psoriasis, psoriatic arthritis, Crohn's disease, and ankylosing spondylitis. The development of antagonists to these mediators has yielded significant clinical benefits in those patients for whom less sophisticated treatments provide little relief.

### Ankylosing Spondylitis

Adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), and secukinumab (Cosentyx) are indicated for ankylosing spondylitis. Although it has been established that anti-TNF $\alpha$  therapies are effective for symptoms of ankylosing spondylitis, it is still unclear whether they prevent structural damage. Current guidelines do not recommend one anti-TNF agent over another, but do recommend monoclonal antibodies over etanercept in cases of recurrent iritis or inflammatory bowel disease.

### Crohn's Disease

Adalimumab (Humira), certolizumab pegol (Cimzia), infliximab (Remicade), and vedolizumab (Entyvio) are indicated in patients with Crohn's Disease. Infliximab is also indicated in reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease, as well as the treatment of children ages 6 years and older. Adalimumab is also indicated in children ages 6 years and older who have had an inadequate response to conventional therapy. Comparative data are lacking; however, adalimumab is specifically indicated for adult patients who are intolerant to or have a diminished response to infliximab. Certolizumab pegol and vedolizumab (Entyvio) are indicated for patients who have had an inadequate response to conventional therapy.

### Cryopyrin-Associated Periodic Syndromes (CAPS)

Canakinumab (Ilaris) and rilonacept (Arcalyst) are both indicated for CAPS associated with FCAS and MWS while anakinra (Kineret) is indicated for CAPS associated with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), a rare periodic fever syndrome which causes uncontrolled inflammation in multiple parts of the body beginning in the newborn period.

### Juvenile Idiopathic Arthritis

Abatacept (Orencia), adalimumab (Humira), and etanercept (Enbrel) are indicated for polyarticular Juvenile Idiopathic Arthritis (JIA) in children 6, 2, and 2 years of age and above, respectively. Tocilizumab (Actemra) is indicated for polyarticular and systemic JIA in children 2 years of age and older. Canakinumab (Ilaris) is indicated for systemic JIA in children 2 years of age and older. Abatacept (Orencia) for JIA must be administered IV for JIA in an outpatient facility. Current treatment guidelines recommend initial therapy with anakinra, glucocorticoid monotherapy, or nonsteroidal anti-inflammatory drugs (NSAIDs) for patients with active systemic disease. Continued disease activity may be treated with canakinumab, tocilizumab, methotrexate, leflunomide, or an anti-TNF agent based on response and initial treatment agent. While agents in this review are not recommended as initial therapy in patients without systemic disease, they may be appropriate as continued therapy based on initial treatment response.

## Rheumatoid Arthritis

The agents in this class approved for treatment of RA are abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), infliximab (Remicade), tocilizumab (Actemra), and tofacitinib (Xeljanz, Xeljanz XR).

Anakinra (Kineret), a IL-1 receptor antagonist, is associated with inferior efficacy and higher toxicity compared with the anti-TNF $\alpha$  therapies. Anakinra is given as monotherapy or in combination with methotrexate or other non-TNF-targeting DMARDs. Infliximab (Remicade) is administered at an outpatient facility as an IV infusion. Abatacept (Orencia) and tocilizumab (Actemra) may be administered either IV in an outpatient facility for RA or may be administered as a SC injection for RA. Tofacitinib (Xeljanz, Xeljanz XR), a Janus kinase (JAK) inhibitor, is approved for patients with an inadequate response or intolerance to methotrexate.

The American College of Rheumatology (ACR) 2015 guidelines for the management of RA recommend more aggressive treatment in patients with early RA (within 6 months of symptom onset) since earlier treatment may provide better outcomes and focus on a treat to target approach. In early RA, combination disease modifying antirheumatic drug (DMARD) therapy, an anti-TNF agent, or a non-TNF biologic (all with or without methotrexate) is preferred over DMARD monotherapy following an inadequate response to DMARD monotherapy.

In patients with established RA, ACR recommends use of DMARD monotherapy over combination therapy or tofacitinib in patients who have never taken a DMARD. If disease activity remains moderate or high despite DMARD treatment, the use of combination DMARDs, an anti-TNF agent, a non-TNF biologic, or tofacitinib (all with or without methotrexate) is preferred over DMARD monotherapy. If disease activity remains moderate or high despite anti-TNF monotherapy, use of a non-TNF biologic (with or without methotrexate) is preferred over another anti-TNF agent or tofacitinib. In general, tofacitinib is recommended as an alternative in the case of multiple anti-TNF and non-TNF biologic failures, and most treatments are appropriate with or without methotrexate. Anakinra was excluded from the guidelines due to infrequent use and limited data.

The 2012 consensus statement on the biologic agents for the treatment of rheumatic diseases from the international Annual Workshop on Advances in Targeted Therapies states that anti-TNF agents used in combination with methotrexate yield better results in the treatment of RA than monotherapy. There is no evidence that any one TNF antagonist should be used before another one can be tried for the treatment of RA or JIA (except with systemic-onset JIA, when anakinra may be effective). There is no evidence that any one TNF antagonist is more effective than any other for the treatment of RA or AS.

## Plaque Psoriasis

Adalimumab (Humira), apremilast (Otezla), etanercept (Enbrel), infliximab (Remicade), ixekizumab (Taltz), secukinumab (Cosentyx), and ustekinumab (Stelara) are approved for the treatment of plaque psoriasis. Cytokine and CAM antagonists indicated for the treatment of psoriasis have similar efficacy.

Etanercept (Enbrel), adalimumab (Humira), ixekizumab (Taltz), secukinumab (Cosentyx), and ustekinumab (Stelara) are given subcutaneously. Infliximab (Remicade) is given by intravenous infusion. Apremilast (Otezla) is an oral tablet given twice daily.

Ustekinumab (Stelara) is an IL-12 and IL-23 antagonist. Ixekizumab (Taltz) and secukinumab (Cosentyx) are interleukin-17A (IL-17A) antagonists which have shown effectiveness against etanercept (Enbrel) and placebo in adults with moderate to severe plaque psoriasis.

The American Academy of Dermatology (AAD) states there is no specific sequence in which anti-TNF agents should be used in patients with moderate to severe chronic plaque psoriasis without psoriatic arthritis. However, the guidelines note that in non-head-to-head phase 3 trials of the individual agents, infliximab clears cutaneous psoriasis in the highest proportion of patients and with the greatest rapidity, followed by adalimumab and then etanercept.

## Psoriatic Arthritis

Adalimumab (Humira), apremilast (Otezla), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), and secukinumab (Cosentyx), and ustekinumab (Stelara) are approved for the treatment of psoriatic arthritis.

Although patients with mild to moderate psoriatic arthritis may be treated with NSAIDs and/or intra-articular steroid injections, the American Academy of Dermatology (AAD) recommends methotrexate, TNF blockade, or the combination of these therapies is considered first-line treatment for patients with moderate to severely active psoriatic arthritis. The clinical trial ACR 20 efficacy data at the primary endpoint with all 6 FDA-approved TNF blockers for the treatment of PsA are roughly equivalent; the choice of which TNF agent to use is an individual one with the degree and severity of cutaneous involvement an important consideration. Apremilast (Otezla) and secukinumab (Cosentyx) have not been included in the current guidelines.

## Ulcerative Colitis

Adalimumab (Humira), golimumab (Simponi), infliximab (Remicade), and vedolizumab (Entyvio) are indicated for treating ulcerative colitis. Infliximab is effective in inducing clinical remission and response in patients with moderate to severe ulcerative colitis with refractory disease, and is also indicated in children  $\geq 6$  years old. Adalimumab and golimumab are approved for inducing and sustaining clinical remission in adult patients with moderate to severe active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine. Golimumab is also approved in patients who have failed to respond to oral aminosalicylates and who cannot tolerate immunosuppressants or aminosalicylates. Vedolizumab (Entyvio) is approved for moderate to severe disease after trial or intolerance to a TNF blocker, immunomodulator, or corticosteroid.

According to the American Gastroenterology Association (AGA), an anti-TNF agent or vedolizumab as monotherapy or combination therapy may be used for maintenance therapy in high-risk outpatients following induction therapy. Induction therapy with these agents may also be considered. Infliximab also has a role in inpatients who have failed IV steroids and for maintenance of remission. Guidelines from the American College of Gastroenterology (ACG) focus on infliximab and consider it an effective choice for maintaining and improving remission as well as in patients with severe colitis with continued symptoms despite optimized corticosteroids. Use of infliximab reduced the need for colectomy in short-term trials.

## Other Indications

Adalimumab (Humira) is also indicated for the treatment of moderate to severe hidradenitis suppurativa (HS), a chronic skin condition that features small lumps under the skin, most commonly where skin rubs together, and can be painful.

Adalimumab (Humira) is also approved for the treatment of non-infectious intermediate, posterior, and panuveitis in adults. It is the only biologic agent approved for this use.

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